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A Review Onvosevi and Hepatitis C

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ABSTRACT

Hepatitis C (HCV) has been contributing to human sufferings tremendously. In the past decade, clinical research in the field of new dosage regimens for HCV has been flourished based on direct-acting antiviral agents (DAA's) with the motive to be safe and efficient in eliminating HCV, thus preventing life-threatening complications. Hepatitis C virus is blood borne, circular and positive stranded virus, comprising of seven different genotypes. Ribavirin and Peg-interferon were considered the backbone of HCV regimens, but advances in the field of Interferon-free DAA's therapy has revolutionized antiviral therapy in treating HCV with cure rates more than 90% for a majority of patients and obtaining efficient safety profile. Despite, an excellent efficacy of DAA's for HCV, treatment failures do occur, so as to overcome this crisis fixed-dose combinations (FDC's) can be employed. Vosevi is FDC tablet approved by USFDA, containing two previously approved drugs Sofosbuvir(NS5B polymerase inhibitor) and Velpatasvir(NS5A inhibitor) which were pan-genotypic in continuation with a new drug, Voxilaprevir(NS3-NS4A protease inhibitor). This triple-drug regimen has SVR up to 96% with all genotypes with the minimum of adverse effects and is the ideal combination in eliminating HCV. This review is the collaboration between historical regimens and currently approved regimens in treating HCV making the treatment streamlined and evidence-based.

INTRODUCTION

Hepatitis C virus (HCV) is being the major threat to the human race. Hepatitis C virus infection has been infecting around 130-200 million people worldwide, which is equal to be 2-3% of world's population [1]. HCV has reported causing more than 3.5lakhs deaths each year due to liver cirrhosis, liver cancer and extra-hepatic manifestations [2]. Hepatitis C virus is the small enveloped virus which belongs to the genus Hepacivirus and family Flaviviridae. The virus is one single strand positive-sense RNA molecule of approximately 9.6kb, the diameter being 50nm [3].The virus is characterized by a remarkable genetic diversity in infected hosts [4].HCV is transmitted through various modes such as injection drug use, unsafe injection practices and transfusion of unscreened blood and blood products [5]. A number of direct-acting antiviral agents are under development for the treatment of chronic HCV infection. These agents block viral production by directly inhibiting one of several steps of HCV lifecycle [6][see figure no1]. Before 2011, Peg-interferon and Ribavirin were considered to be the standard dose regimen in treating HCV [7] with sustained virological rate (SVR) being sub-optimal; that is 45-50% [8]. In 2011, a launch of first DAA's, which are Boceprevir and Telaprevir, first-generation protease inhibitors (PI's) in combination with peg-interferon and Ribavirin(PR), was ideal combination regimen in HCV treatment [9].But as Peg -interferon had many side effects, low SVR, and limited treatment access due to patient's genotype and high pill burden of Boceprevir (12tablets) and Telaprevir (6tablets) daily, made it essential to introduce new peg-INF free fixed-dose combinations regimen for treating HCV[2,10]. In the last quarter of 2014, two fixed-dose combinations were approved by FDA and EMA. The first being Sofosbuvir and Ledipasvir, the second being Paritaprevir boosted by Ritonavir plus Ombitasvir[8].Vosevi - FDC containing sofosbuvir (400mg), telaprevir(100mg) in continuation with voxilaprevir(100mg) is the triple dose tablet administered orally daily for all genotypes for 12weeks[11,12]In Polaris-4 studies, the SVR of vosevi(97%) was superior to Epclusa(90%) and this difference was more pronounced in cirrhotics patients (SVR 96% and 86% respectively)[13].The combination of Sofosbuvir, Velpatasvir, Voxilaprevir, a pan-genotypic third generation NS3/4A Protease inhibitor, offers new treatment options in patients with prior DAA failure and will further strengthen our pan-genotypicarmory against HCV[14].This is USFDA approved Vosevi (Gilead Sciences, INC., Foster City, CA) to treat adults with chronic HCV genotypes 1 through 6 with or without cirrhosis.[15]

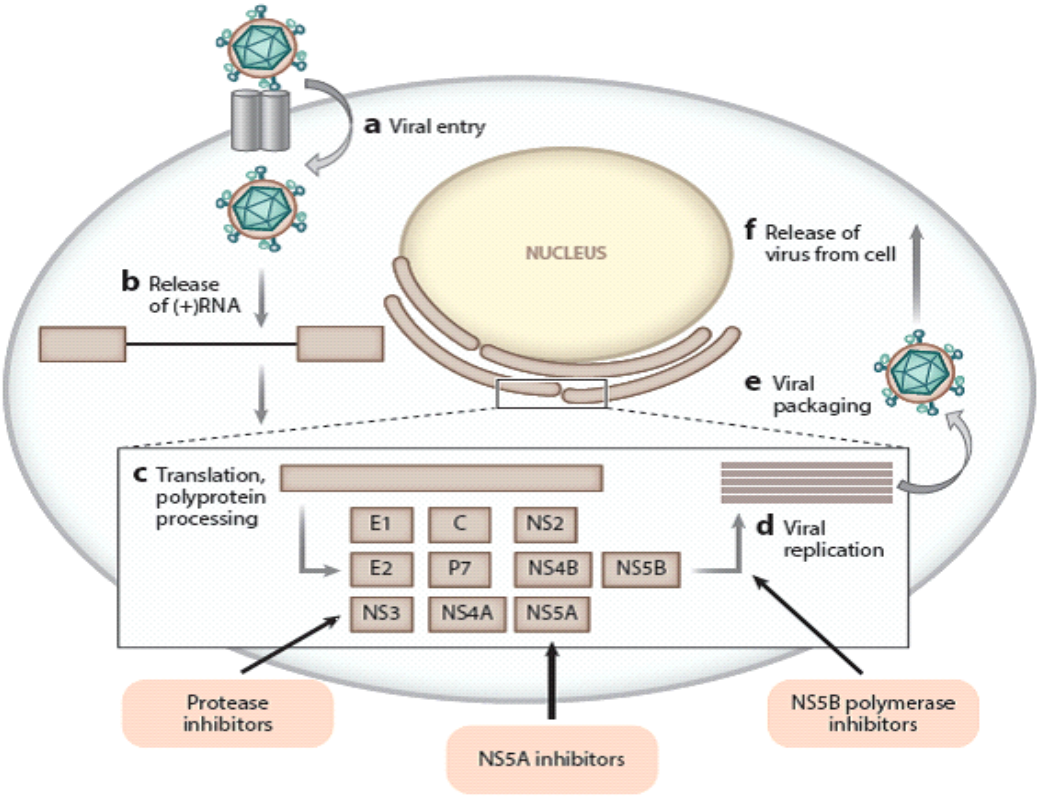

Figure 1

Life cycle of hepatitis C viral infection and targets for mechanism of action for direct-acting antivirals. (*a*) Virus particle–receptor binding and endocytosis; (*b*) cytoplasmic release and uncoating; (*c*) translation and polyprotein processing with structural and nonstructural proteins shown at the endoplasmic reticulum—the site for the mechanism of action of NS3/4 protease inhibitors; (*d*) RNA replication occurring in the membranous web—the site for the mechanism of action of the NS5A inhibitors and NS5B polymerase inhibitors; (*e*) virion packaging and assembly; and (*f*) virion maturation and release.

Figure 1: Life cycle of Hepatitis C viral infection and targets for a mechanism of action for direct-acting antivirals. [See ref no.16]

The old standard treatment used to treat Hepatitis C include drugs like Interferons, Ribavirin, Boceprevir and Telaprevir. Their mechanism of action and side effects are shown in Table No.1

Table 1: Historical drugs used to treat Hepatitis C

Sr. No.	Name of the drug	Mechanism of action	Side effects
1)	Interferons (low molecular weight glycoprotein cytokines)[17]	INF's activate JAK-STAT pathway and stimulate the transcription of specific genes, leading to the synthesis of proteins contributes to viral resistance at different stages of viral infection. Inhibition of protein synthesis is the major effect [18].	Flu-like symptoms Arthralgia Chill's Headaches Fever Myalgia Neurotoxicity Alopecia[18,19]
2)	Ribavirin (purine nucleoside analog has broad-spectrum antiviral activity)[17]	Interfere with the synthesis of guanosine triphosphate, which inhibits capping of viral mRNA [20].	conjunctival irritation, rashes, hemolytic anemia pruritus[18,20]
3)	Boceprevir	Potent inhibition of the HCV NS3A protease[7]	Anemia Neutropenia Dysgeusia[21]
4)	Telaprevir	Potent inhibition of the HCV NS4A protease[7]	Anemia Rashes Anorectal discomfort[21]

The new drugs approved as the combination therapy for Hepatitis C includes, Daklinza, Solvaldi, Epclusa, Harvoni, Olysio, Sovaldi, Technivie Viekira Pak, Viekira XR, Vosevi, Zepatier are given in table no.2 along with their mechanism of action, Duration, SVR & Indications

[See reference 22, 23, 24, 7]

Table 2: Approved new drugs for the treatment of Hepatitis C

Drug Brand Name	Generic name	Indications	Decompensated Cirrhosis	Mechanism of Action	Duration	SVR %
Daklinza® and Solvaldi®	Daclatasvir + sofosbuvir	CHC GT 1 or GT 3	GT 1, 3 with RBV	NS5A inhibitor with a NS5B inhibitor	12 weeks	96-100
Epclusa®	Sofosbuvir/ velpatasvir	CHC GT 1-6	GT 1-6, with RBV	NS5B inhibitor/NS5A inhibitor	12 weeks	93-100
Harvoni®	Ledipasvir/ sofosbuvir	CHC GT 1; GT 4; GT 5; GT 6	GT 1 with RBV	NS5A inhibitor/ NS5B inhibitor	8, 12, or 24 weeks	94-100
Olysio®	Simeprevir	CHC GT 1 in combination with sofosbuvir	Not approved	NS3/4A protease inhibitor	12 -24 weeks	79-81
Sovaldi®	Sofosbuvir	CHC GT 1; GT 2; GT 3; GT 4 Used in combination with other antivirals	Not approved	Nucleotide analog NS5B polymerase inhibitor	12 weeks	Up to 92
Technivie®	Ombitasvir/paritaprevir /ritonavir + ribavirin	CHC GT 4	Contraindicated	NS5A inhibitor/NS3/4A protease inhibitor	12 weeks	97.5
Viekira Pak®	Ombitasvir/paritaprevir/ritonavir + dasabuvir	CHC GT 1	Contraindicated	NS3/4A protease inhibitor/NS5A inhibitor + NS5B inhibitor NS3/4A protease inhibitor/NS5A inhibitor + NS5B inhibitor	12-24 weeks	95-100

Viekira XR®	Ombitasvir/paritaprevir/ritonavir + dasabuvir	CHC GT 1	Contraindicated	NS3/4A protease inhibitor/NS5A inhibitor + NS5B inhibitor	12-24 weeks	95-100
Vosevi®	sofosbuvir/velpatasvir/voxilaprevir	CHC GT 1-6 treatment experienced with NS5A inhibitor; GT 1a or 3 treatment experienced with sofosbuvir and without an NS5A inhibitor	Contraindicated	NS5B inhibitor/NS5A inhibitor/NS3 protease inhibitor	12 weeks	96
Zepatier ®	Elbasvir / grazoprevir	CHC GT 1; GT 4	Contraindicated	NS3/4A protease inhibitor/ NS5A inhibitor	12 or 16 weeks	92-97

- Abbreviations: CHC = chronic hepatitis C; GT = genotype, RBV: ribavirin

Vosevi- fixed-dose combination :

Vosevi @ Gilead is a triple-drug fixed-dose tablet containing direct-acting antiviral agents, Sofosbuvir,Veltapasvir, and Voxilaprevir approved for patients who have failed previously treated with DAA's especially NS5A inhibitor-based regimen. In Phase 3 Polaris-1 trial, Vosevi was compared for 12weeks to placebo in patients with genotypes 1-6 infection who had previously failed HCV regimen containing an NS5A inhibitor. 96% of patients retreated with Vosevi achieved SVR 12[25,26] (SVR 12 is Sustained Virologicrate, also known as a virologic cure, defined as an undetectable viral load at 12 weeks after completion of therapy)[27]

Mechanism of action:

As Vosevi is triple fixed-dose combination it's mechanism of action will differ from the generic drugs present:

Sofosbuvir: it is a nucleotide prodrug which undergoes intracellular metabolism and gets converted to uridine analog triphosphate, which when incorporated into HCV RNA by the NS5B polymerase acts as chain terminator[28]

Velpatasvir: an inhibitor of the HCV NS5A protein, which is required for viral replication. Resistance selection in cell culture and cross-resistance studies indicate velpatasvir targets NS5A as its mode of action.[29]

Voxilaprevir: is a novel, macrocyclic, pan-genotypic, reversible NS3/4A protease inhibitor (PI) [30]

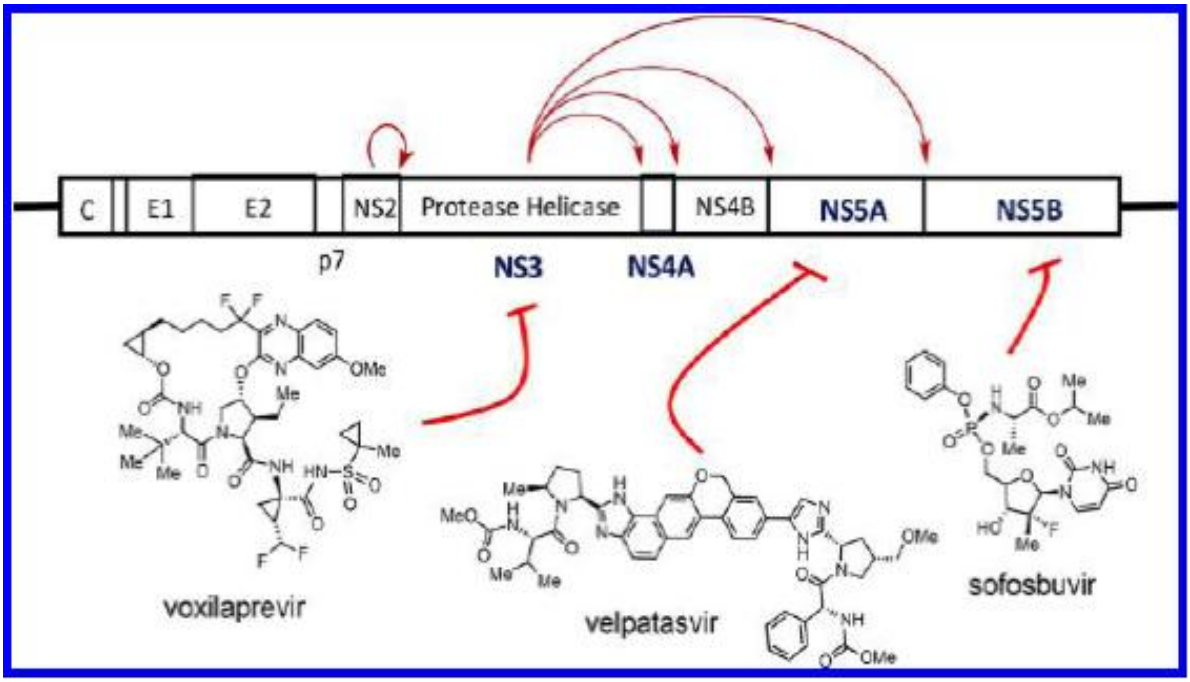

Figure 2: Schematic representation of Mechanism of action of Vosevi [See reference no.31]

Pharmacokinetics of Vosevi:

- Tmax of Sofosbuvir, Velpatasvir, and Voxilaprevir were found to be 2hours, 4hours and 4hours respectively [29]

- Cmax(ng/ml) of Sofosbuvir, Velpatasvir, and Voxilaprevir were found to be 35.4, 56.1, and 85.8 respectively[29]

- Plasma protein binding of Sofosbuvir, Velpatasvir and Voxilaprevir were found to be 61-65%, > 99,>99[29,32]

- Route of elimination of Sofosbuvir, Velpatasvir, and Voxilaprevir are extrahepatic and biliary excretion respectively [29,32]

- Sustained Virologic Rate of Vosevi was found to be 96% respectively [25,26]

Drug Interactions of Vosevi:

- Amiodarone has long half-life, hence should undergo cardiac monitoring before taking Vosevi[26]

- Contraindicated in patients with decompensated cirrhosis [25]

- Contraindicated in patients on rifampin therapy[12]

- Medications that are inducers of these metabolic pathways (eg, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rifabutin, rifapentine, St John's Wort) may decrease therapeutic concentrations of voxilaprevir and should be avoided.[30]

- Mild gastrointestinal upset, including nausea and diarrhea, were reported but were not severe enough to discontinue treatment.[33]

CONCLUSION

Based on all the above-mentioned data and references, we can conclude that the newly approved fixed-dose tablet containing triple drugs is the only recommended tablet which can be used for patients who have failed prior treatment with DAA's regimen for HCV with efficient SVR rates, and negligible drug interactions and side effects, and has outranked the other historic regimens making the HCV regimen streamlined and evidence-based.

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