New Direct Acting Antiviral Agents for the Treatment of Hepatitis C: 2016 and Beyond

Muhammad Umar and Tayyab Saeed Akhter

ABSTRACT

Hepatitis C is one of the commonest public health problems with 130 million people infected worldwide and the burden is increasing. Previously, Interferon along with Ribavirin was the mainstay of treatment but it was associated with toxic side effects. An all-oral regimen with higher rates of sustained viral response (SVR), minimal side effects and no restriction for liver fibrosis staging, was long awaited. Several all-oral interferon-free direct acting antiviral agents (DAAs) have now been approved by FDA for different genotypes of HCV. These include Sofosbuvir, Ledipasvir, Daclatasvir, Simeprevir, Dasabuvir, Ombitasvir, Paritaprevir and Ritonavir. These agents are also available in different combinations commercially under various trade names. A number of studies have proved their efficacy and the AASLD and EASL guidelines recommend several options for each genotype in different categories including treatment naïve, relapers, failure, compensated and decompensated cirrhosis. The purpose of this article is to review the persistently changing treatment regimens for hepatitis C and to simplify the dynamicity of the subject and selection of appropriate regimen for these patients.


INTRODUCTION

Since its discovery in 1989, chronic hepatitis C virus infection has become the most common public health problem. There are more than 130 million people worldwide and the burden of liver disease has significantly increased during the last few decades. In USA alone there are 3.9 million cases of chronic HCV. Usually being asymptomatic, more than 50 - 80% individuals are unaware of their disease.3

Chronic hepatitis C is the most common cause of cirrhosis and the commonest indication of liver transplant in Europe, North and South America, Australia, Japan, Egypt, India and Pakistan. The risk of developing cirrhosis ranges from 5 to 25% over the period of 20 - 30 years.4 Conventional interferon monotherapy has been used since 1991 followed by Pegylated Interferon (PEG) plus ribavirin (RBV) in 2001. In pivotal clinical trial, sustained virological response (SVR) of 40 - 45% was achieved in treatment of genotype 1, upto 80% in genotype 2, and only 50% in genotype 3a. All these therapies left about 50 - 60% of patients as either non-responders or relapers.5 The ideal regimen should have all-oral medicines, once daily dosage, short duration, minimal side effects, pan genotype coverage and high SVR > 95% regardless of liver fibrosis, prior response to IFN / RBV, gender, race and age.6

Since 2011, there has been a major development in hepatitis therapies including drugs that directly act on HCV structural proteins and are called the directly acting agents (DAAs). With the addition of Boceprevir and Telaprevir to the Pegylated Interferon / Ribavirin triple therapy, SVR rate of genotype 1 chronic hepatitis C infection increased from 30 to 43%7-9 to 65 - 75%.10,11 In 2013, the treatment advanced further with release of first nucleotide polymerase inhibitor Sofosbuvir (SOF) and second generation protease inhibitor Simeprevir (SMV). These agents improved the SVR rate of genotype up to 90 - 100%. The interferon free regimen of SOF and RBV is now available for genotype 2 and 3 patients and proves to be effective particularly for genotype 2 with SVR rate 100%; and SVR of upto 65 - 80% in genotype 3.12-14

Literature review strategy: PubMed was searched using the MeSH terms “Hepatitis C, Chronic/drug therapy”, “Direct acting antivirals” and “all-oral regimens for hepatitis C”. The search was filtered to English language articles related to humans only. A total of 378 articles, including original articles, abstracts and review articles, were screened. The studies within the past 5 years emphasising on the all-oral regimen were mainly selected. Important older publications with common references were included but articles, which focused on interferon therapy only, were not considered. Thirty-nine articles were shortlisted and scrutinised in detail to formulate this article. The latest guidelines of American Association for the Study of Liver Disease (AASLD)15 and European Association for the Study of Liver (EASL)16 were also reviewed for updating the existing information on the topic.

Direct acting antiviral agents sofosbuvir: The first...
Summary of studies of interferon-free regimens in patients infected with HCV genotype 2 and 3.

Table I: Summary of studies of interferon-free regimens in patients infected with HCV genotype 2 and 3.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Treatment</th>
<th>SVR12 Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELECTRON</td>
<td>Naïve + treatment experienced</td>
<td>SOF/RBV x 12 weeks</td>
<td>GT2 100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF</td>
<td>GT3 -</td>
</tr>
<tr>
<td>FISSION</td>
<td>Treatment Naïve</td>
<td>SOF/RBV x 12 weeks</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF</td>
<td>56%</td>
</tr>
<tr>
<td>POSITRON</td>
<td>Interferon intolerant</td>
<td>SOF/RBV x 12 weeks</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RBV</td>
<td>61%</td>
</tr>
<tr>
<td>FUSION</td>
<td>Treatment failure</td>
<td>SOF/RBV x 12 weeks</td>
<td>86%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF/RBV x 16 weeks</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RBV</td>
<td>62%</td>
</tr>
</tbody>
</table>

SVR12 = Sustained viral response after 12 weeks of completion of therapy; GT = Genotype; SOF = Sofosbuvir; RBV = Ribavirin.

A trial using SOF/RBV was ELECTRON study that showed SVR of 84% in 25 treatment-naïve patients after 24 weeks of therapy (SVR24). In a subsequent study, SOF and RBV for 24 weeks in 60 genotype 1 naïve patients with poor prognostic factors achieved SVR24 of 68%. In ELECTRON study, SOF/RBV was also used in genotype 2 and 3 patients without cirrhosis and 100% achieved SVR24. In the FISSION trial, SOF/RBV for 12 weeks in 499 naïve patients achieved SVR12 of 97% for genotype 2 patients but in genotype 3, the SVR12 rates were 56% only. Similarly, in POSITRON trial, SVR24 rates after 24 weeks of treatment were 61% for genotype 3 and 93% for genotype 2, respectively in non-cirrhotic patients. Comparative analyses of different trials have been summarised in Table I. Data from authors' own center, presented at DDW 2016 annual congress, showed a RVR of 94.4% in genotype 3 patients.

Sofosbuvir and Ledipasvir: In October 2014, FDA approved a combination of SOF 400 mg with Ledipasvir (LDV) 90 mg as a single pill. The ION study phase III trial included 1952 patients with genotype 1 infection, 1512 were naïve and 224 had compensated cirrhosis. Treatment with 12 weeks for non-cirrhotics or 24 weeks for cirrhotics, regardless of previous therapy or concurrent use of RBV, showed SVR12 rate of 93 - 97.7%. Similarly, in LONESTAR trial, the SVR12 was 100% with 8 or 12 weeks of therapy with or without RBV, irrespective of previous treatment with Boceprevir or Telaprevir or presence or absence of compensated cirrhosis.

Daclatasvir and Sofosbuvir: Daclatasvir is a NS5A inhibitor that has potent pan-genotype activity. Sulbowashi et al. in a phase II trial on patients with genotype 1, 2 or 3 using Daclatasvir and Sof with or without RBV for 24 weeks showed SVR12 of 98%. Another study, from Japan used a combination of Daclatasvir and Asunaprevir for genotypes 1 - 6. The SVR24 was 87.4% for PEG ineligible patients and 80.5% for previously PEG non-responders.

Simeprevir and Sofosbuvir: FDA approved SMV with PEG and RBV for genotype 1 treatment. Three major studies QUEST, PROMISE and ASPIRE using SMV and PEG/RBV in all categories patients: treatment-naïve, experienced and null responders, showed a SVR12 of 80% (cirrhotics showed a lower SVR rate of 60 - 65%). In the phase 2 Cosmos study, SVR12 was 96% regardless of cirrhosis, length of treatment (12 vs. 24 weeks) and with or without RBV. However, prolonged therapy for 24 weeks is recommended in cirrhotic patients by AASLD guidelines. In another study, Sarene V reported SVR12 of 91% in patients with Child Pugh A cirrhosis and SVR12 of 73% in Child Pugh B/C. Competitive analyses of different DAAs for genotype 1 have been summarised in Table II.

Table II: Summary of studies of interferon-free regimens in patients infected with HCV genotype 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Treatment</th>
<th>SVR12 rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ION</td>
<td>Treatment naïve</td>
<td>SOF/Ledipasvir x 12 wk</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF/Ledipasvir + RBV x 12 wk</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Treatment experienced</td>
<td>SOF/Ledipasvir x 12 wk</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF/Ledipasvir + RBV x 12 wk</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF/Ledipasvir x 24 wk</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF/Ledipasvir + RBV x 24 wk</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>Treatment naïve</td>
<td>SOF/Ledipasvir x 8 wk</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF/Ledipasvir + RBV x 8 wk</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF/Ledipasvir x 12 wk</td>
<td>95</td>
</tr>
<tr>
<td>COSMOS</td>
<td>Prior null responders</td>
<td>SOF/SMV x 12 wk</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>(METAVIR F0-F2)</td>
<td>SOF/SMV + RBV x 12 wk</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF/SMV x 24 wk</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF/SMV + RBV x 24 wk</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>Treatment naïve and prior null</td>
<td>SOF/SMV x 12 wk</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>responders (METAVIR F3-F4)</td>
<td>SOF/SMV + RBV x 12 wk</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF/SMV x 24 wk</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SOF/SMV + RBV x 24 wk</td>
<td>93</td>
</tr>
<tr>
<td>AVIATOR</td>
<td>Treatment naïve</td>
<td>3D x 12 wk</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3D + RBV x 12 wk</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Null responder</td>
<td>3D + RBV x 12 wk</td>
<td>93</td>
</tr>
<tr>
<td>SAPPHIRE</td>
<td>Treatment naïve</td>
<td>3D + RBV x 12 wk</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Treatment experienced</td>
<td>3D + RBV x 12 wk</td>
<td>96</td>
</tr>
</tbody>
</table>

SVR12 = Sustained viral response after 12 weeks of completion of therapy; SOF = Sofosbuvir; RBV = Ribavirin; SMV = Simeprevir; SVR = Sustained viral response; GT = Genotype; METAVIR F0-F2 = Non-cirrhotics; METAVIR F3-F4 = Cirrhosis.

In the phase 2 Cosmos study, SVR12 was 96% regardless of cirrhosis, length of treatment (12 vs. 24 weeks) and with or without RBV. However, prolonged therapy for 24 weeks is recommended in cirrhotic patients by AASLD guidelines. In another study, Sarene V reported SVR12 of 91% in patients with Child Pugh A cirrhosis and SVR12 of 73% in Child Pugh B/C. Competitive analyses of different DAAs for genotype 1 have been summarised in Table II.

3D regimen: This is a potent combination of three DAAs including ABT 450, a protease inhibitor, boosted with Ritonavir, Dasabuvir ABT 333, a non-nucleoside RNA polymerase inhibitor and Ombitasvir ABT 267, a NS5A inhibitor. The AVIATOR trial results showed the treatment naïve patients who were treated with 3D regimen plus RBV had SVR24 of 88 - 94% in response to 8 - 12 weeks of treatment. SVR12 of 89% was achieved in the non-RBV group.

Paritaprevir and Dasabuvir/Ombitasvir and Ritonavir: SAPPHIRE-I and II studies are multi-centre randomized...
C-Worthy phase II trials
FDA has recently used this combination in 845 These are the patients who have not been using this combination for 12 weeks. 39 A SVR12 of 97% showed a SVR12 of 99% in patients with genotypes approved this pangenotype combination. ASTRAL-1 another phase III trial, Foster showed a SVR 12 of 99% for the regime due to side effects.35-38

Fatigue only. One percent of the patients discontinued the regime due to side effects.35-38

Sofosbuvir and Velpatasvir: FDA has recently approved this pangenotype combination. ASTRAL-1 showed a SVR12 of 99% in patients with genotypes 1,2,4,5 and 6 using this combination for 12 weeks.42 In another phase III trial, Foster showed a SVR12 of 99% for genotype 2 patients and 95% in genotype 3 patients, respectively after treatment with sofosbuvir + Velpatasvir for 12 weeks.43 Curry et al. used this combination in another trial on decompensated patients for 12 weeks and the SVR12 was 94% and 83% with and without ribavirin, respectively.44

Recommended regimens of DAAs by genotype: After reviewing all the DAAs in the previous section, final recommendations were made in light of AASLD and EASL guidelines along with literature and data from different studies.15,16

Management of HCV infection for treatment-naïve or relapers: These are the patients who have not been treated before at all or if treated previously, have achieved undetectable viral load with IFN/RBV therapy once but relapsed after discontinuing therapy.

**1. Genotype 1:**

i. Recommended regimen I: This regimen includes Elbasvir (50 mg) + Grazoprevir (100 mg) daily for 12 weeks.

ii. Recommended regimen II: This regimen includes SOF (400 mg) + Velpatasvir (100 mg) daily for 12 weeks.

iii. Recommended regimen III: This regimen includes Daclatasvir (60 mg) + SOF (400 mg) daily for 12 weeks.

iv. Recommended Regimen IV: This regimen includes Ledipasvir (90 mg) + SOF (400 mg) daily for 12 weeks.

v. Recommended regimen V: Paritaprevir (150 mg) + Ritonavir (100 mg) + Ombitasvir (25 mg) + weight-based RBV for 12 weeks.

vi. Recommended regimen VI: This regimen includes SOF (400 mg) + SMV (150 mg) for 12 weeks.

**2. Genotype 2:**

i. Recommended regimen I: This regimen includes SOF (400 mg) + Velpatasvir (100 mg) daily for 12 weeks.

ii. Recommended regimen II: This regimen includes Daclatasvir (60 mg) + SOF (400 mg) daily for 12 weeks.

iii. Recommended regimen III: This regimen includes SOF (400 mg) + weight-based RBV for 12 weeks.

Although this regimen is no longer recommended by AASLD guidelines; but in regions where the first two combinations are not available, this regimen is still the only option.

**3. Genotype 3:**

i. Recommended regimen I: This regimen includes Daclatasvir (60 mg) + SOF (400 mg) daily for 12 weeks.

ii. Recommended regimen II: This regimen includes SOF (400 mg) + Velpatasvir (100 mg) daily for 12 weeks.

iii. Recommended regimen III: This regimen includes Elbasvir (50 mg) + Grazoprevir (100 mg) daily for 12 weeks.

iv. Recommended regimen IV: This regimen includes Ledipasvir (90 mg) + SOF (400 mg) for 12 weeks.

**4. Genotype 4:**

i. Recommended regimen I: This regimen includes Paritaprevir (150 mg) + Ritonavir (100 mg) + Ombitasvir (25 mg) + weight-based RBV for 12 weeks.

ii. Recommended regimen II: This regimen includes SOF (400 mg) + Velpatasvir (100 mg) daily for 12 weeks.

iii. Recommended regimen III: This regimen includes Elbasvir (50 mg) + Grazoprevir (100 mg) daily for 12 weeks.

iv. Recommended regimen IV: This regimen includes Ledipasvir (90 mg) + SOF (400 mg) for 12 weeks.

**5. Genotype 5 or 6:**

i. Recommended regimen I: This regimen includes SOF (400 mg) + Velpatasvir (100 mg) daily for 12 weeks.

ii. Recommended regimen II: This regimen includes Ledipasvir (90 mg) + SOF (400 mg) for 12 weeks.

Management of HCV infection for treatment failure: This category includes the patients who have already received a treatment for hepatitis C but either they were partial responders or did not respond at all. Partial responders by definition are the patients with > 2 log_{10} IU/ml decline but their virus remains detectable at 24 weeks or by the end of treatment.

**1. Genotype 1:**

i. Recommended regimen I: This regimen includes Elbasvir (50 mg) + Grazoprevir (100 mg) daily for 12 weeks.

ii. Recommended regimen II: This regimen includes Daclatasvir (60 mg) + SOF (400 mg) daily for 12 weeks.

iii. Recommended regimen III: This regimen includes Daclatasvir (60 mg) + SOF (400 mg) daily for 12 weeks.

iv. Recommended regimen IV: This regimen includes Ledipasvir (90 mg) + SOF (400 mg) for 12 weeks.
recommended for those who failed to respond to SOF + RBV + IFN therapy in past.

v. Recommended regimen V: Paritaprevir (150 mg) + Ritonavir (100 mg) + Ombitasvir (25 mg) + twice-daily Dasabuvir (250 mg) + weight-based RBV for 12 weeks. For Genotype 1b patients RBV can be avoided.

vi. Recommended regimen VI: This regimen includes SOF (400 mg) + SMV (150 mg) for 12 weeks.

2. Genotype 2:

i. Recommended regimen I: This regimen includes SOF (400 mg) + Velpatasvir (100 mg) daily for 12 weeks. For patients who have experienced SOF/RBV combination in the past, RBV should be added in the regimen.

ii. Recommended regimen II: This regimen includes Daclatasvir (60 mg) + SOF (400 mg) for 12 weeks. For patients who have experienced SOF/RBV combination in the past, RBV can be added in the regimen and it should be extended for 24 weeks.

iii. Recommended regimen III: SOF (400 mg) + weight-based RBV for 16 weeks or 24 weeks, whereas SOF (400 mg) + weight-based RBV + weekly PEG-IFN for 12 weeks is only for IFN eligibles and can also be given to patients who failed to respond to SOF + IFN in past. These combinations are no more recommended by AASLD but can be considered in regions where the new DAAs are currently unavailable.

3. Genotype 3:

i. Recommended regimen I: Daclatasvir (60 mg) + SOF (400 mg) daily for 12 weeks is for those who failed to respond to IFN + RBV. But for patients who failed to respond to SOF + RBV, the regimen should be used for 24 weeks with weight-based RBV.

ii. Recommended regimen II: This regimen includes SOF (400 mg) + Velpatasvir (100 mg) daily for 12 weeks. RBV should be added for SOF/RBV experienced cases.

iii. Recommended regimen III: SOF (400 mg) + weight-based RBV + weekly PEG-IFN for 12 weeks is for those who are IFN eligible and can be used both for patients who fail to respond to IFN + RBV or SOF + RBV therapy in past. Although no more recommended by AASLD; but in resource-poor countries like Pakistan where genotype 3 is prevalent, it should be considered till new combinations are available.

4. Genotype 4:

i. Recommended regimen I: This regimen includes Paritaprevir (150 mg) + Ritonavir (100 mg) + Ombitasvir (25 mg) + weight-based RBV for 12 weeks.

ii. Recommended regimen II: This regimen includes SOF (400 mg) + Velpatasvir (100 mg) daily for 12 weeks.

iii. Recommended regimen III: This regimen includes Elbasvir (50 mg) + Grazoprevir (100 mg) + weight-based RBV daily for 16 weeks.

iv. Recommended regimen IV: This regimen includes Ledipasvir (90 mg) + SOF (400 mg) for 12 weeks.

5. Genotype 5 or 6:

i. Recommended regimen I: This regimen includes Ledipasvir (90 mg) + SOF (400 mg) for 12 weeks.

ii. Recommended regimen II: This regimen includes SOF (400 mg) + Velpatasvir (100 mg) daily for 12 weeks.

DAA regimens for compensated cirrhosis: This special population was waiting for recommendations of the experts for the use of DAAs in cirrhotics as fibrosis is considered an important prognostic factor in determining the SVR.45 Recent studies with DAA, although focusing on genotype I, have promising results in this group of patients.46

Genotype I compensated cirrhotic patients: A phase-II COSMOS study by Lawitz et al. showed SVR rate of 94 - 100% in genotype 1 of cirrhotic patients by using SOF + SMV for 12 and 24 weeks with and without RBV.47 Poordad et al. in cirrhotic patients showed a SVR12 rate of 92% in child class A and 94% in child class B by using Daclatasvir + SOF + RBV for 12 weeks.33 Afshal and Zeuzem showed in ION-2 study, a SVR12 of 86% in treatment experienced cirrhotics with SOF and ledipasvir combination and 98% for 24 weeks duration.22,23,48 In the LONFSTAR study, Lawitz reported >95% SVR in genotype 1 cirrhotics as well as in protease inhibitor failure patients with SVR of 100%.49 In 2014, results of TURQUOISE-2 study a combination of Paritaprevir, Ritonavir, Ombitasvir and Dasabuvir with RBV for 12 or 24 weeks in genotype 1 naïve and treatment-experienced cirrhotics, the SVR12 rate was 92 - 96% respectively.50

i. Recommended regimen I: This regimen includes Elbasvir (50 mg) + Grazoprevir (100 mg) daily for 12 weeks. For cirrhotic patients, RBV can be added as an alternative regimen, but the duration needs to be extended for 16 weeks.

ii. Recommended regimen II: This regimen includes SOF (400 mg) + Velpatasvir (100 mg) daily for 12 weeks.

iii. Recommended regimen III: Daclatasvir (60 mg) + SOF (400 mg) + weight-based RBV daily for 24 weeks is only recommended for treatment failures who used IFN and RBV in the past.

iv. Recommended regimen IV: Ledipasvir (90 mg) + SOF (400 mg) for treatment naïves/relapers is given for 12 weeks. For treatment failures, either the duration is increased for 24 weeks or weight-based RBV is added for 12 weeks (1a or 1b) or 24 weeks (1a only). The RBV based 24 weeks treatment can also be used for SOF + RBV failures.

v. Recommended regimen V: Paritaprevir (150 mg) + Ritonavir (100 mg) + Ombitasvir (25 mg) + twice-daily Dasabuvir (250 mg) + weight-based RBV is recommended for 24 weeks for genotype 1a; whereas for genotype 1b, same regimen is given without RBV for 12 weeks.

vi. Recommended regimen VI: This regimen includes SOF (400 mg) + SMV (150 mg) + RBV for 12 weeks and if the regimen is to be used without RBV, the duration can be extended to 24 weeks.
Genotype 2 and 3 compensated cirrhotic patients: The FISSION study using SOF+RBV in genotype 2 naïve cirrhotics showed SVR rate of 100% and in previously treated patients, a SVR rate of 78% with 12 weeks therapy.\textsuperscript{14,51} The FUSION study of treatment experienced patients for 12 vs. 16 weeks duration did not show any extra benefit for extended treatment.\textsuperscript{20}

In genotype 3 naïve cirrhotics, the VALENCE study using combination of SOF/RBV for 24 weeks showed SVR\textsubscript{12} of 92% and SVR\textsubscript{12} of 62% in treatment experienced cirrhotic patients.\textsuperscript{52} In ALLY 3, the combination of SOF + Daclatasvir for 12 weeks showed a SVR of 58% in naïve and 69% in treatment failure genotype 3 cirrhotics.\textsuperscript{53} In the ASTRAL-3 study combination of SOF + Velpatasvir for 12 weeks in naïve cirrhotics showed a SVR of 93% and in treatment experienced cirrhotics 89% respectively.\textsuperscript{43} Finally in genotype 3 cirrhotics, the addition of PEG IFN still seems to improve SVR rate.\textsuperscript{51}

**Genotype 2:**

i. Recommended regimen I: This regimen includes Daclatasvir (60 mg) + SOF (400 mg) daily for 16 to 24 weeks. For patients who have experienced SOF/RBV combination in the past, RBV can be added in the regimen and it should be extended for 24 weeks.

ii. Recommended regimen II: This regimen includes SOF (400 mg) + Velpatasvir (100 mg) daily for 12 weeks. For patients who have experienced SOF/RBV combination in the past, RBV should be added in the regimen.

iii. Recommended regimen III: This regimen includes SOF (400 mg) + weight-based RBV for 16 weeks. For treatment failures, regimen can be extended to 24 weeks as well. If the treatment failure patients are IFN eligible then adding weekly PEG-IFN can reduce the duration to 12 weeks as well. Although this regimen is no longer recommended by AASLD, but it can be practised till the availability of above mentioned drugs in certain part of the world.

**Genotype 3:**

i. Recommended regimen I: Daclatasvir (60 mg) + SOF (400 mg) + weight-based RBV daily for 24 weeks but for patients with treatment failure who used IFN + RBV or SOF + RBV in the past, RBV must be added.

ii. Recommended regimen II: This regimen includes SOF (400 mg) + Velpatasvir (100 mg) daily for 12 weeks. For treatment failures, RBV should be added to the regimen.

iii. Recommended regimen III: This regimen includes SOF (400 mg) + weight-based RBV + weekly PEG-IFN for 12 weeks; but for IFN ineligible patients, SOF (400 mg) + weight-based RBV can be used for 24 weeks. Although this regimen is no longer recommended by AASLD, but it can be practised till the availability of above mentioned regimens in certain part of the world.

**Genotype 4 compensated cirrhotic patients:** In Egypt, genotype 4 cirrhotic patients treated with SOF + RBV for 24 weeks showed a SVR rate of 100%.\textsuperscript{54} In NIAID SYNERGY study, patients with genotype 4 having adverse fibrosis treated with Ledipasvir and SOF for 12 weeks showed SVR rate of 95%.\textsuperscript{55}

EASL guidelines 2014 preliminary recommended Daclatasvir + SOF + RBV as well as Paritaprevir/Ombitasvir/Ritonavir for the treatment of genotype 4 cirrhotic patients for 24 weeks.\textsuperscript{54}

i. Recommended regimen I: This regimen includes Paritaprevir (150 mg) + Ritonavir (100 mg) + Ombitasvir (25 mg) + weight-based RBV for 12 weeks.

ii. Recommended regimen II: This regimen includes SOF (400 mg) + Velpatasvir (100 mg) daily for 12 weeks.

iii. Recommended regimen III: This regimen includes Ledipasvir (90 mg) + SOF (400 mg) daily for 12 weeks. For treatment failures, RBV should be added for 16 weeks.

iv. Recommended regimen IV: This regimen includes Ledipasvir (90 mg) + SOF (400 mg) for 12 weeks. For treatment failures, RBV should be added to the regimen.

**Genotype 5 and 6 compensated cirrhotic patients:** There are limited studies available for genotype 5 or 6. Very small number of patients with genotype 5 or 6 is reported from NEUTRINO study using SOF and all patients achieved 100% SVR rate\textsuperscript{14}. However, ASSLD guidelines recommend SOF + Ledipasvir for 12 weeks.\textsuperscript{56,57}

i. Recommended regimen I: This regimen includes Ledipasvir (90 mg) + SOF (400 mg) for 12 weeks.

ii. Recommended regimen II: This regimen includes SOF (400 mg) + Velpatasvir (100 mg) daily for 12 weeks.

Management of HCV infection in patients with decompensated cirrhosis: Before the advent of DAAs, treatment of HCV was out of question for decompensated patients as IFN-based regimens can be used in compensated cirrhosis.

<table>
<thead>
<tr>
<th>Recommended regimen</th>
<th>Genotype 1 or 4</th>
<th>Genotype 2 or 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Daclatasvir (60 mg) + SOF (400 mg) + RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks</td>
<td>Daclatasvir (60 mg) + SOF (400 mg) + RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks</td>
</tr>
<tr>
<td>II</td>
<td>SOF (400 mg) + Velpatasvir (100 mg) + RBV (initial dose of 600 mg for child class C) for 12 weeks</td>
<td>SOF (400 mg) + Velpatasvir (100 mg) + weight-based RBV for 12 weeks</td>
</tr>
<tr>
<td>III</td>
<td>Ledipasvir (90 mg) + SOF (400 mg) + RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks</td>
<td></td>
</tr>
</tbody>
</table>

**Table III:** Treatment of HCV infection in patients with decompensated cirrhosis.

**Note:** For Genotype 1 or 4 if the patient is RBV ineligible, then all 3 regimens can be extended for 24 weeks without RBV.

SOF = Sofosbuvir; RBV = Ribavirin.
worsen the liver status. Whether eradicating HCV in decompensated patients will have a long-term beneficial effect is not known yet, but on short-term basis it reduces the need for liver transplant in this group of population. In SOLAR 1 phase II trial, the combination of Ledipasvir, Sof and RBV for 12 weeks produced high rates of SVR12 in patients with advanced liver disease, including those with decompensated cirrhosis before and after liver transplantation. Another trial used Velpatasvir/SOF combination in decompensated patients for 12 weeks and the SVR12 was 94% and 83% with and without Ribavirin, respectively.

According to AASLD guidelines, the recommended Regimens in decompensated cirrhosis are tabulated in Table III.

CONCLUSION

DAAs are efficacious and safe for both compensated and decompensated hepatitis C related chronic liver disease. More and more trials will further improve the outcome of the disease. Furthermore, the effect of these DAAs is yet to be analysed for eastern populations. It is expected that these agents will altogether change the spectrum of hepatitis C related diseases in near future.

As newer DAAs are being approved for hepatitis C therapy at faster rate, the recommended regimens are changing rapidly. With the advent of DAAs like Grazoprevir, Elbasvir and Velpatasvir, the rate of sustained viral eradication is approaching 100% with pan genotypic effect, shorter duration of therapy like 8 or 12 weeks, improved tolerability and minimum side effects.

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