

Treatment Options for HCV Genotype-4

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Abstract

For the last three decades, HCV infection had been a challenging health problem due to high prevalence rate, fatal complications and till recently the lack of effective treatment. In the pre directly acting agents (DAAs) era, the interferon-ribavirin based treatment was of limited success in the clearance of the virus compounded by major side effects that caused significant morbidity and poor quality of life lasting several months based on the long duration of treatment. Patients with advanced hepatic fibrosis responded poorly to treatment and were far more susceptible to the side effects which at times proved fatal. The new DAAs with their high potency, tolerability and relative short duration of treatment are transforming the landscape of HCV management. The potential of HCV eradication over the coming decades has become a feasible target in many parts of the world. HCV genotype has always been an important predictor of response and an essential determinant for the duration of treatment. Genotype-4 is the predominant genotype in the Middle East particularly Egypt and Gulf region. Clinical trials on genotype-4 are limited especially in the era of directly acting antiviral agents. This review summarizes the treatment options for HCV genotype-4 infection based on available evidence and international HCV treatment guidelines.

Keywords: Gastroenterology; Hepatology; Cirrhosis; Fibrosis

Introduction

The treatment of Hepatitis C virus (HCV) has come a long way since its discovery in 1989 [1] and there has not been a clearer prospect to the path of its eradication. HCV patients have been suffering from its long-term and often fatal complications and waited long for a cure by a safe and effective treatment. Being an important health problem with over 170 million infected patients all over the world [2,3], a great attention has been given to HCV infection and the milestones of HCV treatment development demonstrated a slow yet a steady improvement in response rate. It is however the better understanding of the life cycle of HCV that has made the greatest impact [4]. Recognition of various structural and non-structural proteins with better understanding of RNA polymerase replicative role have led to the development of potent inhibitors to viral replication with the added benefit of high safety profile and relatively shorter duration of treatment [5]. Growing evidence is showing a significant increase in sustained virological response rate (SVR) in HCV infected patients in general with some variation among subgroups based on the presence of cirrhosis, treatment experience, co-infections, post organ transplantation, end stage renal disease (ESRD) and HCV genotypes.

HCV genotypes follow a certain geographical distribution whereby genotypes 1, 2 and to a lesser extent 3 are common in USA and Europe while genotype 4 patients are clustered in the middle east, particularly Egypt and Saudi Arabia. Genotype 5 is seen commonly in northern parts of South Africa while genotype 6 is predominantly common in South East Asia [6,8]. There is a paucity of data and publications on the population affected by genotype-4. The available data from recent randomized clinical trials albeit small have shown that in genotype-4, the response to the new DAAs is very similar to genotype-1. The first generation protease inhibitors, namely telaprevir and boceprevir,

though they demonstrated a significant improvement in treating genotype-1 HCV compared to pegylated interferon /ribavirin (PEGINF/RBV) regimen, they were not of benefit in genotype-4 patients [9]. Cultural and socioeconomic factors when taken into consideration might also have an impact of the patient-treatment interaction and subsequently the overall response to therapy [10]. These along with other factors, such as genetic variation, make it imperative to have more research in parts of the world where genotype-4 is prevalent.

Having reached the era of directly acting antiviral agents (DAAs), physicians looking after HCV genotype-4 infected patients are in need to have solid data on the best options for treating these patients. International liver diseases organizations have published guidelines on treatment options for HCV genotype-4 but they were mostly based on small clinical trials or extrapolation from the trials on genotype-1. There are subgroups of genotype-4 patients in whom data are particularly scarce such as the cirrhotics and organ transplant patients.

This review will highlight the treatment options for HCV genotype-4 based on the best available evidence and the published HCV treatment guidelines and will address the areas of future research.

HCV Genotype-4 Treatment Options

Pegylated interferon plus Ribavirin (PEGINF/RBV)

Although Interferon (INF) is not anymore a preferred option by both patients and physicians due to its nasty side effects and relatively low response rate, it remains one of the valuable tools in countries with limited resources where the very expensive DAAs are not affordable. Since its introduction in 2001, Pegylated Interferon (PEGINF) was considered the standard of care in combination with ribavirin (RBV)

and was found in several trials to be superior to conventional INF [11]. Few years after getting FDA approval, several studies were published on HCV genotype-4 patients from Middle East and they were primarily from Egypt and Saudi Arabia using PEGINF/RBV combination [12,15]. These studies showed similar efficacy to that seen in genotype-I patients with comparable safety profile. Alfaleh et al. reported an SVR rate of 43% in patients treated with PEGINF alpha 2b and fixed dose RBV for 48 weeks compared to 32% in patients treated with conventional INF with RBV [13]. El Makhzangy et al. reported a relatively higher response rate on Egyptian patients treated with PEGINF alpha 2a and weight adjusted RBV with an SVR rate that reached 61% [15]. The difference in response rate was not clearly explained but the use of higher RBV dose, the difference in subgenotypes and the type of PEGINF could be contributing factors. The latter was shown in a head to head trial comparing PEGINF alpha 2a and alpha 2b by Kamal et al. where the former was found to be more effective in treating HCV genotype-4a (SVR rate 70.6 vs 54.6% respectively, $p=0.017$) [16]. Some of these trials included cirrhotic and treatment experienced patients and they were reported to have much lower response rate [12].

Several predictors were looked at to optimize the response to treatment and tailor treatment duration. Genetic factors were the most frequently studied and IL28 phenotypes were repeatedly found to predict response to treatment with CC being the most favorable phenotype associated with over 80% response rate in those treated with PEGINF/RBV [17]. Viral dynamics were also found to correlate with SVR and in patients who achieved rapid virological response (viral load below detection at week 4) SVR rate can be as high as 86% when treated for 24 weeks only [18]. Effect of subtypes was however not well studied. Treatment of HCV in special population (HIV, hematological diseases) was tried in small-uncontrolled cohorts and mostly shown to have comparable efficacy with more toxicity [19,20].

Pegylated interferon plus Ribavirin and DAAs

Several DAAs have been approved for treatment of HCV infection. Phase 3 trials however included either no or small number of genotype-4 patients. Based on these data, most of the DAA are considered in the guidelines for treatment of HCV genotype-4. Larger studies are needed to confirm these findings and until then there is a general acceptance among hepatologists that DAAs will be as effective as in genotype-1 patients. Several protocols have been proposed and used, some with PEGINF and some are INF free.

Sofosbuvir, a nucleotide analog inhibitor of hepatitis C virus NS5B polymerase, in combination with PEGINF/RBV was one of the earliest regimens studied. ATOMIC trial was a randomized open label phase II trial that examined the efficacy of several sofosbuvir based regimens in treatment of naïve, non-cirrhotic HCV patients with genotypes 1, 4, 5 and 6. Eleven genotype-4 patients were included in the trial and 9 (82%) achieved SVR24. The study investigated different durations and the SVR rate was comparable between groups (87-89%). All patients in ATOMIC received at least 12 weeks of PEGINF/RBV [21]. This finding was confirmed in phase III NEUTRINO trial that again included small number of genotype-4 patients. Neutrino is an open label trial that included naïve HCV patients with genotype 1, 4, 5 and 6. Seventeen percent of the patients had compensated cirrhosis and all patients were treated with sofosbuvir 400 mg OD, PEGINF and weight based RBV for 12 weeks. Of the 28 genotype-4 patients, 27 patients achieved SVR12. Treatment was well tolerated and was completed by 98% of participants while serious adverse events were reported in 1% [22]. Large real life studies are still awaited however a recently published

small study from Germany have shown a high SVR rate with sofosbuvir based triple therapy (83.3%) although lower than that reported from clinical trial [23]. As always, presence of cirrhosis is a negative predictor for response and as with PEGINF/RBV [22]. Recent analysis of another real-life cohort of 119 patients treated with sofosbuvir based triple therapy have shown an important correlation with viral kinetics since patients who did not achieve undetectable HCV-RNA at week 4 had SVR rate of less than 30% [24].

Simeprevir, a second-generation NS3/4A protease inhibitor, showed activity against genotype 1 and 4. FDA approved it for treatment of both genotypes. Moreno et al. evaluated the efficacy and safety of simeprevir combined with PEGINF/RBV in a phase III, open label, single arm study (RESTORE) that included 107 genotype-4 patients. The study included naïve and treatment experienced patients and 29% of patient had cirrhosis. Naïve patients and partial relapsers received response guided therapy with simeprevir 150 mg daily for 12 weeks and PEGINF/RBV for 24-48 weeks based on their week 4 RNA (24 weeks if RNA <25 IU/ml and 48 weeks if RNA >25 IU/ml). On the other hand all partial and null responders received 12 weeks of simeprevir and 48 weeks of PEGINF/RBV. The overall SVR rate was 65% but it varied significantly based on response to prior treatment, since naïve patients and relapsers achieved SVR in 83% and 86% respectively; while SVR was lower in partial and non-responder 60% and 40% respectively. Adverse events (AEs) were mainly grade 1 and 2; serious AEs were infrequent (4.7%) and considered unrelated to simeprevir [25].

Daclatasvir, a potent NS5A inhibitor, was found to be very effective in phase IIb trial against HCV genotype-4 with an SVR rate that reached 100% when 60 mg of daclatasvir for 12 weeks was given with PEGINF/RBV for 24-36 weeks (response guided therapy) [26]. In phase III study (COMMAND-4), daclatasvir 60 mg was used in combination with PEGINF/RBV for 24 weeks if RNA is undetectable at week 4 or 48 weeks if RNA is detectable at week 4. Study included 124 naïve HCV genotype-4 patients (82 patients in treatment arm and 42 in control arm) and 11% had cirrhosis. Overall SVR Rate was 82%, and in patients who achieved undetectable RNA at week 4 was 86%. The safety and tolerability profile of daclatasvir arm was comparable to control arm and the discontinuation rate was 4.9% in patients who received daclatasvir plus PEGINF/RBV and 7.1% in control arm who received PEGINF/RBV alone [27].

Another NS3 protease inhibitor, asunaprevir, was found to exert additional antiviral activity when combined with daclatasvir. The efficacy of this combination together with PEGINF/RBV was examined in a phase III open label trial (HALLMARK-QUAD). The study included genotype-1 (354 patients) and genotype-4 (44 patients), who had prior null or partial response to PEGINF/RBV. All patients received daclatasvir 60 mg, asunaprevir 100 mg, PEGINF alpha 2a and weight based RBV for 24 weeks. Genotype-1 patients achieved SVR12 in 93% while it was 100% in genotype-4. Serious adverse events were reported in 6% and discontinuation rate was 5% [28]. Table 1 summarizes the most important clinical trials on genotype-4 patients using INF-based regimens.

Interferon-free regimens

Interferon-free or all-oral regimens are becoming more attractive options for treatment of HCV infection owing to their convenient use, high safety profile and shorter duration. These regimens however are very expensive and their access is not feasible in several parts of the world [29].

Trial (yr)	Regimen	Sample size	Patients	SVR rate
ATOMIC21 Phase II, randomized open-label	SOFO+PEGINF+RBV For 12 or 24 wks	9 pts	Naïve, Non-cirrhotic	82%
NEUTRINO22 Phase III, open-label trial	SOFO+PEGINF+RBV For 12 wks	28 pts	Naïve Cirrhosis (17%)	96%
Wehmeyer23 Real-life study	SOFO+PEGINF+RBV For 12 wks	24 pts	Naïve and Rx experienced	83.3%
RESTORE25 Phase III, open-label trial	SMV 12 wks+ PEGINF+RBV (for 24-48 wks, RGT in naïve and relapsers, and for 48 wks in partial and null responders)	107 pts	Naïve and Rx experienced Cirrhosis (29%)	Overall: 65% Naïve: 83% Relapser: 86% Partial: 60% Null: 40%
COMMAND-427 Phase III, Randomized, placebo-controlled trial	DCV 12 wks+ PEGINF/RBV (for 24-48 wks, RGT)	82 pts	Naïve Cirrhosis (11%)	82%
HALLMARK-QUAD28 Phase III, open-label trial	DCV+ASV+ PEGINF+RBV For 12 wks	44 pts	Rx experienced Cirrhosis (46%)	Overall: 98%

Sofos: Sofosbuvir, SMV: Simeprevir, DCV: Daclatasvir, ASV: Asunaprevir, PEGINF: Pegylated interferon, RBV: Ribavirin.

Table 1: Clinical trials on the use of DAAs in treatment of HCV genotype 4, INF-Free Regimens.

Several combinations of DAAs have been used in clinical trials and have shown very high efficacy in eradication of HCV. Some of these trials however were small and therefore it is very important to look at larger real life studies when evaluating the efficacy and safety of these products.

Sofosbuvir is considered the backbone for most of the interferon free regimens being the only approved NS5B inhibitor. In combination with other agents from the same and other manufacturers, very high response rate was achieved with excellent safety profile and subsequently, high adherence rate to the treatment [30]. When combined with RBV, sofosbuvir was found to be effective in treating HCV genotype 1 and 4 in HIV co-infected patients [31]. Shorter duration of treatment was needed for genotype-2, but for others 24 weeks of treatment was mostly needed to achieve an acceptable SVR rate. In Genotype-4, sofosbuvir 400 mg and weight based RBV combination for 24 weeks was found to be safe and effective in treating patients of Egyptian ancestry with an overall SVR rate of 93%. Treatment was well tolerated and there was no discontinuation of treatment [32]. This result was replicated in a real life study from Egypt that included 103 patients, 17% with cirrhosis and SVR12 was 90% in 24 weeks group. Cirrhotics achieved lower SVR rate (78%) compared to 93% in patients without cirrhosis [33].

Sofosbuvir and simeprevir combination with or without RBV were studied in COSMOS trial which was a phase IIa open label randomized trial. The study included two cohorts of genotype-1 patients. Cohort I had non-responders with low fibrosis score (Metavir F0-2) while cohort II included naïve and non-responders with advanced fibrosis (Metavir F3 and F4). In both cohorts patients were randomized to four groups based on duration (12 vs. 24 weeks) and RBV administration. High SVR rate was achieved in the sofosbuvir/simeprevir 12 weeks group (93% in both) compared to 24 weeks (93% in cohort I and 100% in cohort2). No added benefit was found with the addition of RBV to

this regimen in both cohorts [34]. The trial did not include genotype-4 patients yet experts felt that the result could be extrapolated to this group of HCV patients and the regimen was considered appropriate by some international guidelines for treatment of HCV genotype-4 patients. The real-life data from French Observational Cohort included 119 genotype-4 patients who were monoinfected with HCV and received sofosbuvir and simeprevir with or without RBV for 12-24 weeks. Patients treated for 12 weeks without RBV had SVR in 84% while those treated for 24 weeks with or without RBV or 12 weeks with RBV achieved 100% SVR12 [35]. More recently, OSIRIS (phase IIa) trial was presented in AASLD 2015 meeting. The trial was conducted in Egypt and it showed that combination of sofosbuvir/simeprevir without RBV for 12 weeks could achieve an SVR12 of 100% in cirrhotic and non-cirrhotic HCV genotype-4 patients while 8-weeks regimen was less effective with SVR12 of 75% [36].

A combination of sofosbuvir and daclatasvir was another all-oral regimen studied in genotypes 1-3 patients. After 12 weeks of treatment, SVR was achieved in 100% of naïve genotype-1 patients and 90 and 95% in treatment experienced patients treated with and without RBV respectively [37]. Again the trial did not include genotype-4 patients, but majority of hepatologists might consider it an excellent treatment option knowing that both agents are very active against HCV genotype-4 in INF based trials.

The novel, one tablet, combination of sofosbuvir and ledipasvir is gaining a lot of popularity in treatment of HCV infection. It was FDA approved for treatment of HCV genotype-1. The convenience of use, short duration of treatment and the high efficacy and safety profile made this combination the preferred option by a lot of physicians and highly accepted by patients. Unfortunately, as with other DAAs, the trials on genotype-4 are so limited with small number of patients. The 12 weeks course of this combination was found very effective in genotype-I patients with a response rate that exceeded 95% in non-

cirrhotic patients [38]. The result was replicated in a phase IIa trial on genotype-4 since all the patients enrolled in the study and completed the 12 weeks course (20 patients) achieved SVR when they were treated with 12 weeks of sofosbuvir/ledipasvir. Six patients with cirrhosis were included in the trial. The treatment was well tolerated and no discontinuation of medicine was reported [39]. The study on patients with advanced liver disease (SOLAR-1) however included much smaller number of genotype-4 patients. Four out of 5 patients treated with sofosbuvir/ledipasvir and RBV for 12-24 weeks achieved SVR. It is very difficult to make a conclusion on this result due to heterogeneity of patients and different treatment duration. Results on more than 330 genotype-1 patients however were impressive with an overall SVR rate of 96-98% in patients without cirrhosis or with compensated cirrhosis, 85-88% in patients with moderate hepatic impairment and 60%-75% in patients with severe hepatic impairment [40].

The combination of ombitasvir, ritonavir and paritaprevir was used in one of the largest cohorts of genotype-4 in the era of DAAs.

PEARL-1, a phase IIb randomized open label trial, enrolled 135 HCV genotype-4, non- cirrhotic patients. Of the 86-naïve patients, 42 were randomly assigned to receive the combination with RBV while 44 patients had it without RBV. The cohort also included 49 treatment-experienced patients who received RBV containing regimen. After 12 weeks of treatment, 100% of naïve patient who had RBV containing regimen achieved SVR compared to 90.9% in the RBV free regimen. Similarly, all treatment experienced patients achieved SVR. This might indicate the importance of RBV when using this combination. The treatment was well tolerated with no adverse event related discontinuation of the medication [41]. This combination when used with RBV was also found very effective in HCV genotype-4 with compensated (child A) cirrhosis. AGATE 1 is a phase III, multi-center open label trial with 2 parts. Part 1 was presented in AASLD 2015 meeting and showed that combination of ombitasvir/paritaprevir/ritonavir with weight based RBV for 12 and 16 weeks resulted in SVR12 of 97 and 100% respectively [42]. This combination is not recommended in patients with decompensated cirrhosis.

Trial (yr)	Regimen	Sample size	Patients	SVR rate
Egyptian Ancestry 32 Phase II, randomized, open-label Trial	SOFO+RBV for 12 or 24 wks	60 pts	Naïve and Rx experienced Cirrhosis (23%)	12 wks: 68% 24 wks: 93%
Doss et al. [33] Real-life data	SOFO+RBV for 24 wks	103	Naïve and Rx experienced Cirrhosis (17%)	Overall: 90% Cirrhotics: 78% No Cirrhosis: 93%
French Observational Cohort 35 Real-life Data	Sofos+SMV ± RBV for 12-24 wks	119 pts	Naïve and Rx experienced	12 wks: 84% 24 wks: 100%
NIAID SYNERGY38 Phase IIa trial, open- label study	SOFO+LDV for 12 wks	21 pts	Naïve and Rx experienced Cirrhosis (28.6%)	Overall: 95% Naïve: 92% Rx experienced: 100%
SOLAR-139 Phase II, open-label	SOFO+LDV+RBV for 12 or 24 wks	5 pts	Decompensated Cirrhosis	80%
PEARL-140 Phase IIb, Randomized, open-Label study	Ombatesvir+ritonavir+paritaprevir ± RBV For 12 wks	135 pts	Naïve and Rx experienced	With RBV: 100% No RBV: 90.9%
Asselah et al. [42] Pooled Data	Grazoprevir+elbasvir ± RBV for 12 wks	103 pts	Naïve and Rx experienced Cirrhosis (16.5%)	Naïve: 97% Rx experienced: 86%

Table 2: Clinical trials on the use of DAAs in treatment of HCV genotype 4, INF-Free Regimens.

Last but not the least, the combination of grazoprevir (NS3/4A protease inhibitor) and elbasvir (NS5A inhibitor) was found very effective against HCV genotype 1, 4 and 6. All genotype-4 patients (18 pts) achieved SVR after receiving a fixed-dose grazoprevir 100 mg/ elbasvir 50 mg for 12 weeks [43]. A pooled data on genotype-4 patients treated with grazoprevir-elbasvir with or without RBV that was presented in AASLD 2015 have shown high efficacy of this combination since 97% of naïve and 86% of treatment experienced patients achieved SVR [44]. Grazoprevir/elbasvir combination got FDA approval in Jan 2016 for treatment of chronic HCV genotype 1 and 4 and being a RBV free regimen makes it an excellent option for cirrhotic patients in whom RBV use is not preferred.

More real-life data are expected to come from Middle East countries on the use of DAAs in genotype-4 patients. In the last AASLD meeting, one study from Qatar has examined the efficacy and safety of two INF-free regimens, Sofosbuvir/daclatasvir and Sofosbuvir/Simeprevir on 85 patients and SVR4 was achieved in 96% of them [45]. Table 2 summarizes the most important trials on genotype-4 patients using INF-free regimens. Table 3 summarizes the clinical guidelines from American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of Liver Diseases (EASL) on treatment of HCV genotype-4 infection [46,47].

	Naive	Rx experience	Compensated Cirrhosis	Decompensated cirrhosis
AASLD (2015)	<p>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks. (IIb-B).</p> <p>Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV for 12 weeks. (I-B).</p> <p>Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks. (IIa-B).</p> <p>Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks. (II-B)</p> <p>Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV for 12 weeks. (IIb-B).</p>	<p>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks. (IIa-B)</p> <p>Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV for 12 weeks. (IIa-B)</p> <p>Daily sofosbuvir (400 mg) for 12 weeks and daily weight-based RBV plus weekly PEG-IFN for 12 weeks for patients who are eligible to receive IFN. (IIa-B)</p> <p>Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks. (IIa-B)</p>	<p>Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks (IIa-B).</p>	<p>Daily daclatasvir (60 mg), sofosbuvir (400 mg), and low initial dose of RBV (600 mg, increased as tolerated) for 12 weeks (II-A)</p> <p>Daily fixed-dose combination ledipasvir (90 mg)/ sofosbuvir (400 mg) and RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks. (IIb-C).</p> <p>Daily daclatasvir (60 mg) and sofosbuvir (400 mg) for 24 weeks is recommended for patients who are RBV intolerant or ineligible. (IIb-C)</p> <p>Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) and low initial dose of RBV (600 mg, increased as tolerated) for 24 weeks is recommended for patients in whom prior sofosbuvir-based treatment has failed (IIb-C)</p>
EASL (2015)	<p>A combination of weekly PegIFN-α, daily weight based ribavirin and daily sofosbuvir (400 mg) for 12 weeks (B1)</p> <p>A combination of weekly PegIFN-α, daily weight based ribavirin (for 24-36 weeks depending on week 4 response) and daily simeprevir (150 mg) for 12 weeks (B1)</p> <p>A fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) once daily (A1)</p> <p>A fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) for 12 weeks with daily weight-based ribavirin</p> <p>A combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) 12 weeks (B2)</p> <p>A combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks (B2)</p>	<p>Those who failed treatment with Pegylated INF and ribavirin can be treated like naive patients.</p>	<p>A fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) once daily with weight based ribavirin for 12 weeks (B1) or for 24 weeks without ribavirin (B1).</p> <p>A fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) in one single tablet (two tablets once daily with food), for 12 weeks with daily weight-based ribavirin (A1).</p> <p>A fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) for 24 weeks with daily weight-based ribavirin (B1)</p> <p>A combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) and weight based ribavirin for 12 weeks (B2) or without ribavirin for 24 weeks (B2)</p> <p>A combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for and weight based ribavirin for 12 weeks (B2) or without ribavirin for 24 weeks (B2)</p>	<p>A fixed-dose combination of sofosbuvir and ledipasvir with weight based ribavirin for 12 weeks or without ribavirin for 24 weeks (B1)</p> <p>A combination of sofosbuvir and daclatasvir with weight-based ribavirin, for 12 weeks or without ribavirin for 24 weeks(B1)</p>

Table 3: International guidelines on treatment of HCV genotype 4 infection.

Which Regimen to be Used?

Choosing the best regimen for treating HCV genotype-4 patients might vary from one place to another depending on the available agents, patient condition and physician preference. Most of the available options can achieve high SVR rate (>90%) with an excellent safety profile however the high cost of DAA might limit the number of these options. Presence of cirrhosis, particularly with decompensation and potential drug-drug interaction will render some regimens unsuitable. Prioritizing patients based on disease stage seems necessary in many countries where treatment availability for all HCV infected patients is not warranted.

In patients with decompensated cirrhosis, the combinations of sofosbuvir/daclatasvir or sofosbuvir/ledipasvir with low dose RBV for

12 weeks are recommended. In patients who are RBV intolerant, extending treatment to 24 weeks will be needed to give a similar response rate. Sofosbuvir/ledipasvir with weight based RBV for 12 weeks is an excellent option in patients with compensated cirrhosis however sofosbuvir/simeprevir combination for 12-16 weeks might be preferred being an RBV free regimen.

Several options with comparable efficacy are available for non-cirrhotic patients and what might favor one over the others are the number of tablets, duration of treatment, cost, drug-drug interaction and availability. Sofosbuvir/ledipasvir, being a one tablet daily regimen, makes it a preferable option by most of the patients. Other regimens including ombitasvir/ritonavir/paritaprevir plus RBV, sofosbuvir/simeprevir, sofosbuvir/daclatasvir and grazoprevir/elbasvir can be used for 12 weeks with very high SVR rate. In places where resources are

limited, the combination of PEGINF/RBV with sofosbuvir for 12 weeks is an option if patient can tolerate INF.

Future Directions

We have seen tremendous success in the treatment of chronic HCV infection. There are still major challenges ahead. The proportion of those treated is only a fraction to the ones who are waiting treatment. More, less than 25% of patients with HCV have been identified in developed countries and this percentage is much lower in endemic parts of the world. It is therefore very important to improve the early diagnosis of infected patients through education, mass screening and better referral system. A tremendous effort from governments is needed to make the access to treatment possible to all patients and particularly to those who are at risk of disease complication. A shorter duration of treatment in carefully selected group of patients (young, low fibrosis stage) will definitely reduce the cost of treatment and improve patient compliance.

Conclusions

The recent revolution in development of highly selective antiviral agents has made a major impact on treatment of HCV. With more effective and less toxic DAAs and substantial shortening of treatment duration, the eradication of HCV is becoming a more realistic target to achieve. Large clinical trials have demonstrated high efficacy of most of the DAAs on genotype-1 however more studies are needed for better evidence of efficacy and safety in genotype-4 patients. There is a particular need for large real life studies in areas where genotype-4 is prevalent. Last, the cost of these medications remain prohibitive particularly in countries with poor per capita income and special programs in collaboration with WHO are needed to improve the accessibility to this drugs and in turn helps in the long term objective of eradicating this infection.

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