Review Article

The New Era of Hepatitis C Virus Therapy

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ABSTRACT

The hepatitis C virus (HCV) has a significant medical and economic impact on societies around the world, and it has been estimated that 130-180 million people are infected with HCV. Therapies for HCV are currently undergoing a revolution. In recent years, several new treatments have been approved by the United States Food and Drug Administration, and many other treatments are in phase II or III clinical trials, including direct antiviral agents (DAAs). Due to recent major advances in the field of HCV therapy, a summary of findings on new HCV therapies are provided in this review article, including reports on new DAAs.

Key Words: Cirrhosis and null responders, direct antiviral agents, hepatitis C virus

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The prevalence of HCV worldwide is 2–3%, representing 130–180 million infected individuals.[1-3] Patients who are infected with HCV are at a risk of developing serious complications such as liver cirrhosis, hepatocellular carcinoma, and liver failure.[4-8] Several studies have suggested that the prevalence of HCV is higher in Asia (2.1%, 83 million patients) and Africa (3.2%, 28 million patients) than in other countries, and Egypt has the highest prevalence of HCV (15%).[1,2] In contrast, the lowest reported prevalence of HCV is in the United Kingdom (<1%).

In Saudi Arabia, the estimated prevalence of HCV reported by the WHO in 2012 was 1.8%.[9] However, in a cross-sectional study of 74,662 individuals, the average prevalence of HCV among young individuals was 0.33%.[10] HCV genotype 4 is the most prevalent HCV genotype in Saudi Arabia (60%), followed by genotype 1 (25.9%).[11] The geographical distribution of HCV genotype 4 is shown in Figure 1.

HCV is the leading cause of HCC and liver transplantation worldwide, and thus it has had a significant medical and economic burden.[12-16] It has been estimated that the direct annual cost of HCV treatment (excluding the cost of antiviral therapy) in Canada will reach $258 million dollars in 2032,[17] which represents an alarming estimate of the future disease burden in Canada. Other countries will likely have a similar future disease burden, and the situation could be worse in countries with higher disease prevalence, such as Egypt.

Several HCV management guidelines have been published, including guidelines by the American and European Association for the Study of Liver Diseases.[18-24] However, major advances have occurred in HCV therapy in recent years. In this review article, a summary of the recent studies and findings on HCV management will be provided, including regimens utilizing direct antiviral agents (DAAs).

Direct antiviral agents

Multiple therapeutic agents were developed to target different steps in the HCV life cycle [Figure 2]. Telaprevir and boceprevir were the first NS3/4A serine protease inhibitors.[25] Followed by simeprevir (NS3/4A protease inhibitor) that was approved in 2013 for the management of HCV in combination with PEG-IFN and RBV.[26] Sofosbuvir was the first nucleotide NS5B polymerase inhibitor that has been approved with ledispavir (NS5A) in the management of HCV.[27] In addition, the combination of the ritonavir, paritaprevir (the NS5A inhibitor), ombitasvir, and the non-nucleoside polymerase

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inhibitor dasabuvir with or without RBV was approved for patients with HCV genotype 1 and 4.

HCV GENOTYPE 1

Previously, PEG-IFN and ribavirin (RBV) administration for 48 weeks was the standard of care for patients with HCV genotype 1. However, PEG-IFN/RBV dual therapy has a poor sustained virologic response rate (SVR) (40%–50%).[28] In 2011, boceprevir and telaprevir (the first DAAs) were approved for the management of patients with HCV genotype 1.[29,30] Boceprevir/telaprevir-based triple therapy has a better SVR rate compared with dual therapy. However, these NS3/4A protease inhibitors have a significant toxicity, potential drug–drug interactions and low response rate among experienced cirrhotic individuals.[31-33]

In addition, it must be used with PEG-IFN and RBV. In 2013, a second generation of DAAs (including simeprevir) was approved for use in combination with PEG-IFN and RBV.[26,34,35] However, simeprevir had a low response rate among cirrhotic patients in whom dual therapy had previously failed. In addition, the SVR of simeprevir was low among patients with HCV genotype 1a who had the K80Q polymorphism.

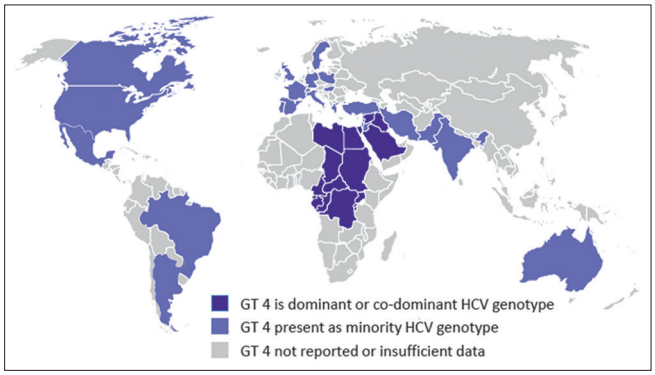
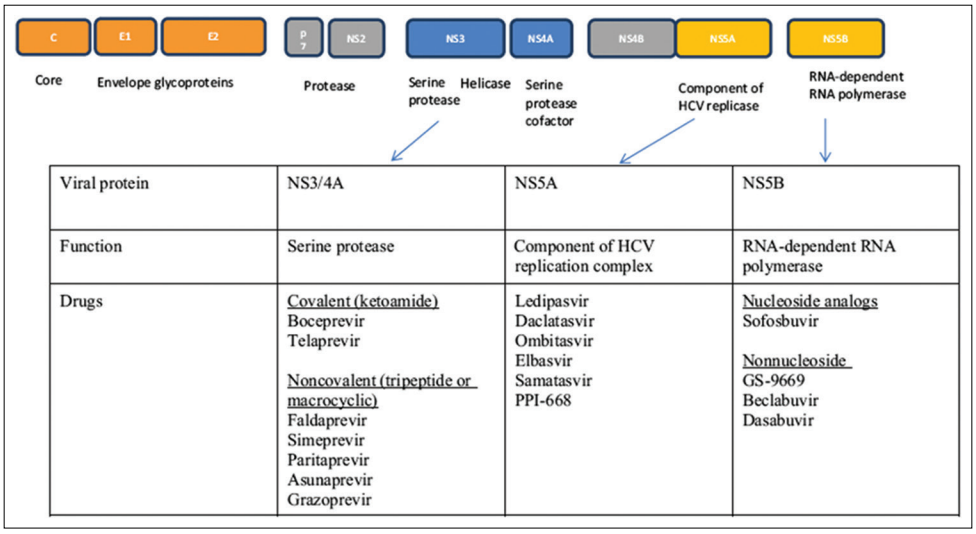


Figure 1: Geographic distribution of HCV genotype 4 infection

Sofosbuvir, the first HCV nucleotide polymerase inhibitor, was approved in 2013 for use in combination with PEG-IFN and RBV.[36] In the NEUTRINO study, sofosbuvir at a daily dose of 400 mg was used in combination with PEG-IFN and RBV for 12 weeks in patients with HCV genotype 1, and the SVR rate was 89%; however, the SVR in patients with genotype 1a was higher than that of patients with genotype 1b (92% vs 82%; nonsignificant trend). In addition, the presence of cirrhosis and IL28B may predict the sofosbuvir SVR rate. In a multivariate analysis, the sofosbuvir SVR rate in patients with cirrhosis was lower than that of noncirrhotic patients (80% vs 92%). In addition, the sofosbuvir SVR rate in patients with the non-IL28B CC genotype was lower than that of patients with the CC genotype (87% vs 98%). Side effects were similar in both the groups (dual therapy vs sofosbuvir-based triple therapy) and only 2% of patients discontinued therapy due to side effects.

In the COSMOS study, two cohorts were enrolled.[37] The first cohort included prior null responders to PEG-IFN and RBV with mild fibrosis (80 patients), and the second cohort included patients who were either treatment-naïve or null responders to dual therapy with advanced fibrosis (87 patients). All patients received a combination of sofosbuvir (400 mg daily) and simeprevir (150 mg daily) with or without RBV for 12 or 24 weeks. The SVR rate ranged from 79% to 100%, without a clear benefit of extended therapy, the use of RBV, or the absence of the K80Q polymorphism. In addition, the SVR rate in null responders was greater than 90%, regardless of fibrosis severity. These promising



Viral protein	NS3/4A	NS5A	NS5B
Function	Serine protease	Component of HCV replication complex	RNA-dependent RNA polymerase
Drugs	Covalent (ketoamide) Boceprevir Telaprevir Noncovalent (tripeptide or macrocyclic) Faldaprevir Simeprevir Paritaprevir Asunaprevir Grazoprevir	Ledipasvir Daclatasvir Ombitasvir Elbasvir Samatasvir PPI-668	Nucleoside analogs Sofosbuvir Nonnucleoside GS-9669 Beclabuvir Dasabuvir

Figure 2: Hepatitis C virus genome and the polyprotein targets of newly approved direct-acting antiviral agents

results were obtained with a small sample size, and a larger study is required to confirm them. However, sofosbuvir and simeprevir are effective in managing patients with HCV genotype 1, especially those who cannot tolerate PEG-IFN, and it has a good safety profile. The discontinuation rate of therapy with sofosbuvir and simeprevir was less than 1% among patients without cirrhosis, as against a rate of 2% in patients with cirrhosis. Most adverse events associated with sofosbuvir and simeprevir occurred in the RBV-treated group.

The combination of 400 mg sofosbuvir (a nucleotide polymerase inhibitor) and 90 mg ledipasvir (NS5A inhibitor) in a single tablet was approved in 2014, and the combination was evaluated in the ION-1, ION-2, and ION-3 trials.[27,38,39] In the ION1 trial, the combination of sofosbuvir and ledipasvir was evaluated in 865 treatment-naïve patients, among whom 136 patients (15.7%) had liver cirrhosis.[38] The patients were randomly assigned to groups that received 12 or 24 weeks of sofosbuvir and ledipasvir with or without RBV. The SVR rate was similar in all treatment groups and ranged between 94% and 99%. There was no clear benefit of extended therapy, use of RBV, presence of IL28B-CC, or absence of cirrhosis. The discontinuation rate for the sofosbuvir/ledipasvir treatment was 3% among patients who were treated for 24 weeks, whereas no patients in the group treated for 12 weeks discontinued treatment. Most of the side effects associated with the sofosbuvir/ledipasvir treatment occurred in the RBV-treated group.

In the ION-3 trial, the combination of sofosbuvir and ledipasvir was evaluated in 647 treatment-naïve, noncirrhotic patients who were randomly assigned to treatment groups that received 8 or 12 weeks of sofosbuvir and ledipasvir, with or without RBV.[39] The overall SVR rates ranged from 93% to 95%, and there was no clear benefit of the use of RBV or the absence of NS5A resistance mutations. However, the relapse rate in the group treated for 8 weeks was higher than that of the group treated for 12 weeks (5% vs 1%). A post hoc analysis was performed to identify patients in whom an 8-week treatment regimen would be sufficient to achieve SVR.[40] In the analysis, the SVR rate was similar in groups of patients with a baseline HCV RNA <6 million IU/mL that were treated for 8 and 12 weeks (97% vs 96%). However, the SVR rate in the group treated for 12 weeks was higher than of the group treated for 8 weeks if the baseline HCV RNA was ≥6 million IU/mL (94% vs 90%). In addition, the relapse rate in the group treated for 8 weeks was higher than that of the group treated for 12 weeks if the baseline HCV RNA was ≥6 million IU/mL (10% vs 1%). Therefore, the United States Food and Drug Administration (FDA) recommends treatment of naïve, noncirrhotic patients with 8 weeks of sofosbuvir and ledipasvir if the baseline HCV RNA is <6 million IU/mL, and 12 weeks of treatment if the viral load is higher.

In a study by Wyles *et al*., sofosbuvir and ledispavir combination regimen was evaluated in 51 patients in whom sofosbuvir-based regimens failed. The patients were treated with sofosbuvir and ledispavir with RBV for 12 weeks, and the SVR ranged from 95% to 100%.[41] Therefore, patients in whom 8 weeks of therapy failed can be retreated for 12 weeks. This promising result suggests treatment of all naïve, noncirrhotic patients with 8 weeks of sofosbuvir and ledispavir, regardless of the patient's baseline viral load. It has been estimated that treating 100 patients for 8 weeks, followed by 12 weeks of retreatment of the estimated nine patients expected to fail therapy, would cost less than that for treating 100 patients for 12 weeks. The duration of therapy can be shortened based on each patient's access to the drug and at the discretion of the health care provider.

In the ION-2 trial, sofosbuvir and ledispavir were evaluated in 440 treatment-experienced patients. The participants were randomly assigned to groups treated with 12 or 24 weeks of sofosbuvir and ledispavir, with or without RBV.[27] Only 20% of the study participants had cirrhosis. Among the noncirrhotic patients, the SVR rate ranged from 95%-100%, and there was no clear benefit of extended therapy or use of RBV. In contrast, among patients with cirrhosis, the SVR after 24 weeks of therapy was higher than the SVR after 12 weeks of therapy (100% vs. 86%), there was no clear benefit of the use of RBV, and more adverse events occurred in the RBV-treated group.[27] Based on this result, the FDA recommended 24 weeks of therapy for treatment-experienced, cirrhotic HCV patients. However, a larger study (SIRIUS) was subsequently performed in 155 treatment-experienced, cirrhotic HCV patients.[42] The patients were randomly assigned to groups that received 12 weeks of sofosbuvir and ledispavir with RBV or 24 weeks of sofosbuvir and ledispavir, and the SVR rates were similar in both groups. Therefore, treatment with sofosbuvir, ledispavir, and RBV for 12 weeks can be used as an alternative to 24 weeks of treatment with sofosbuvir and ledispavir. A summary of management options for HCV genotype 1 is provided in Table 1.

In the SOLAR-1 study, sofosbuvir and ledispavir were evaluated in HCV genotype 1 and 4 patients with decompensated cirrhosis.[43] One hundred and eight patients with Child–Pugh Score B and C were randomized to sofobuvir and ledispavir in combination with RBV for 12 or 24 weeks. The SVR rates were almost similar in both groups (86%–90%), without a clear benefit of the extending of therapy for 24 weeks, the presence of genotype 1b, the presence of IL28B-CC, or the absence of NS5A resistance mutations. The treatment was well tolerated without major side effects.

Daclatasvir (NS5A inhibitor) and sofosbuvir were evaluated in patients with HCV genotype 1.[44,45] Initially, 44 treatment-

Table 1: Summary of clinical trial data in HCV genotype 1 patients

Study (reference)	*n*	Treatment	Duration	SVR (%)	Limitations
ION 3[39]	647	Sofosbuvir and ledispavir	8 weeks	93	Applicable only for treatment naïve, non-cirrhotic patients with viral load <6logs
ION 1,2 and 3[27,38,39]	1305	Sofosbuvir and ledispavir	12-24 weeks	86-99	Suboptimal response with short duration od therapy among experienced, cirrhotic patients
NEUTRINO[36]	291	PEG-IFN, sofosbuvir and RBV	12 weeks	89	Patients who are intolerable to interferon based therapy
COSMOS[37]	168	Simeprevir and sofosbuvir	12 weeks	79-100	Suboptimal response in cirrhotic HCV genotype 1a patients
Sulkowski *et al*[44]	167	Daclatasvir and sofosbuvir	12-24 weeks	98	Lack of evidence in cirrhotic patients
Manns *et al*[46]	307	Daclatasvir and asunaprevir	24 weeks	82-90	Lack of evidence in treatment-experienced patients Lack of efficacy in HCV genotype 1a patients
SAPPHIRE-I[48]	631	Paritaprevir/ritonavir/ ombitasvir, and RBV	12-24 weeks	80-100	RBV must be part of the combo therapy Longer duration of therapy is required especially in treatment-experienced, cirrhotic HCV genotype 1a patients (24 weeks)
C-SALVAGE[51]	79	Grazoprevir/elbasvir and RBV	12 weeks	96-100	Small sample size. However, the study was performed in difficult to treat patients

HCV: Hepatitis C virus, SVR: Sustained virologic response rate, RBV: Ribavirin, PEG-IFN: Pegylated interferon

naïve patients were randomly assigned to treatment groups that received 24 weeks of daclatasvir and sofosbuvir, with or without RBV. Subsequently, the study was expanded to include 123 additional patients with HCV genotype 1 who were randomly assigned to groups that received daclatasvir and sofosbuvir, with or without ribavirin, for 12 weeks (82 treatment-naïve patients) or 24 weeks (41 treatment-experienced patients). Patients with cirrhosis were excluded from the study. The SVR rate was 98% in both groups, and there was no clear benefit of the use of RBV, the presence of genotype 1b, the presence of IL28B-CC, or the absence of NS5A resistance mutations. The most common adverse events were fatigue, headache, and nausea. In addition, daclatasvir was evaluated in combination with asunaprevir in treatment-naïve, treatment-experienced, treatment-intolerant, and treatment-ineligible HCV genotype 1b patients.[46] The 307 treatment-naïve patients in the study were randomly assigned to groups that received 24 weeks of daclatasvir and asunaprevir or placebo. The participants assigned to the placebo group subsequently entered another study evaluating daclatasvir and asunaprevir. All treatment-experienced, treatment-ineligible, and treatment-intolerant patients received 24 weeks of daclatasvir and asunaprevir. Of the patients in the study, 30% had liver cirrhosis. The SVR rate was 90% in the treatment-naïve group and 82% in the treatment-experienced, treatment-ineligible, and treatment-intolerant groups. There was no difference in SVR rate due to IL28B genotype or the presence/absence of liver cirrhosis. Based on this result, daclatasvir and asunaprevir should only be applied in patients with HCV genotype 1b, and a larger sample size is required to assess the efficacy of this combination in treatment-experienced cirrhotic patients. In addition, daclatasvir was evaluated with PEG-IFN and RBV in treatment-naïve patients with HCV genotype 1, and the SVR rate ranged from 89% to 100%. However, this therapy is not appealing because of the significant regimen duration and the necessity of IFN treatment.[47]

In the SAPPHIRE-I study, the effects of paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV were evaluated in treatment-naïve HCV genotype 1 patients.[48] The 631 study participants were randomly assigned to treatment groups that received 12 weeks of 3D and RBV or the placebo. The SVR rate was slightly higher in patients with genotype 1b than in patients with genotype 1a (98% vs. 95%). The discontinuation rate due to adverse events was 0.6%, and the most common side effects were nausea, pruritus, insomnia, diarrhea, and asthenia.[48] In addition, this regimen was evaluated in 380 treatment-naïve and treatment-experienced patients with compensated cirrhosis.[49]

The study participants were randomly assigned to treatment groups that received 12 or 24 weeks of paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV. Among patients with genotype 1b, the SVR rate ranged from 99% to 100%, and no pretreatment predictors were identified. In contrast, in patients with HCV genotype 1a, the SVR rate was slightly higher after 24 weeks of therapy in comparison with 12 weeks of therapy (94% vs 89%), but the result was not statistically significant.[49] However, in null responders with genotype 1a, the 24-week regimen was superior to 12 weeks of therapy (SVR, 93% vs 80%).[49] Based on this result, the US FDA approved this regimen in patients with HCV genotype 1. However, other regimens are more attractive because of a reduced pill burden.

In the C-SWIFT study, grazoprevir (previously MK-5172) was evaluated in 102 treatment-naïve HCV genotype 1 patients.[50]

Treatment-naïve, noncirrhotic patients were randomly assigned to groups that received 4, 6, or 8 weeks of grazoprevir/elbasvir and sofosbuvir. However, treatment-naïve cirrhotic patients were randomly assigned to groups that received 6 or 8 weeks of treatment. The SVR rate in the noncirrhotic group was higher than that of the cirrhotic group. Among the treatment-naïve noncirrhotic patients, the SVR rate after the 6-week regimen was superior to that achieved after 4 weeks of treatment (87% vs 39%). Among the treatment-naïve, noncirrhotic patients, the SVR rate after the 6-week regimen was superior to that achieved after 4 weeks of treatment (87% vs 39%). The most common side effects of the treatment were headache (4%), fatigue (2%), and nausea (2%).

In the C-SALVAGE study, grazoprevir and elbasvir were evaluated in HCV genotype 1 patients who failed previous DAAs.[51] Seventy-nine patients received grazoprevir and elbasvir in combination with RBV for 12 weeks. Forty percent of patients had liver cirrhosis and the SVR rate was 97.5%, without a clear benefit of the presence of genotype 1b, the presence of IL28B-CC, or the absence of NS5A resistance mutations. The most common side effects of the treatment were fatigue (27%), headache (19%), asthenia (15.2%), and nausea (11.1%). This study had an excellent result among difficult-to-treat patients. However, a larger sample size is required to assess the efficacy of this treatment among this subset of patients. In addition, this regimen was evaluated in HCV genotype 1 patients with chronic kidney disease. Two hundred and twenty-four participants were randomized to immediate treatment with grazoprevir and elbasvir for 12 weeks or differed treatment where patients received placebo for 12 weeks then they were enrolled in an open-label study.[52] Only 6% of patients had liver cirrhosis and 20% were treatment-experienced. Seventy-five percent of patients were on dialysis and the SVR rate was 99%, without a clear benefit of the presence of genotype 1b or the presence of IL28B-CC. None of the patients discontinue therapy due to side effects.

The use of faldaprevir (an NS3/4A protease inhibitor) with PEG-IFN and RBV has been evaluated in treatment-naïve patients with HCV genotype 1.[53] In the study, 652 patients were randomly assigned to groups that received PEG-IFN/RBV for 24 weeks or PEG-IFN/RBV/faldaprevir for 12 or 24 weeks. The SVR rate in the faldaprevir-treated group was higher than that of the dual therapy group (80% vs 50%), and there was no clear benefit of extended therapy or an increased dose of faldaprevir.[53] This therapy might be more appealing than simeprevir-based therapy (PEG-IFN, RBV, and simeprevir) because of the duration of the regimen.

HCV GENOTYPE 2

PEG-IFN and RBV was the standard of care in patients with HCV genotype 2 and 3. However, the dual therapy had suboptimal response especially in HCV genotype 3 and the discontinuation rate was between 15% and 20%.[54] The first non–interferon (IFN)-free regimen was evaluated in the FISSION study. In this study, the effectiveness of the use of sofosbuvir and RBV was evaluated in treatment-naïve patients. The participants were randomly assigned to groups that received 24 weeks of PEG-IFN and RBV or sofosbuvir and RBV for 12 weeks.[36] Of the patients in the study, 20% had liver cirrhosis. The SVR rate was 97% in the group treated with sofosbuvir and RBV, and the SVR was 78% in the group treated with PEG-IFN and RBV. There were fewer adverse events in the group treated with sofosbuvir and RBV than those in the group treated with PEG-IFN and RBV. A similar result was found in the VALENCE study, in which the SVR rate ranged from 97% to 100% in the treatment-naïve patients.[55] However, the SVR rate was lower in treatment-experienced cirrhotic patients (88%).[55] Similarly, in the FUSION study, the SVR rate was suboptimal among treatment-experienced cirrhotic patients treated with sofosbuvir and RBV for 12 weeks (60%). However, extending therapy for 16 weeks might improve SVR (78%, not statistically significant).[56] The effectiveness of the use of PEG-IFN, sofosbuvir, and RBV was evaluated in treatment-experienced patients with HCV genotype 2 in an open-label phase 2 study, and the SVR rates were found to be similar in patients with or without cirrhosis. Serious adverse events occurred in four patients, and the majority of the side effects were attributed to PEG-IFN and RBV.[57]

The effectiveness of treatment with sofosbuvir and ledispavir has not been evaluated in patients with HCV genotype 2. However, in a study of sofosbuvir with GS-5816 in treatment-naïve patients with HCV genotype 2, all patients (except one who died during the follow-up period) achieved an SVR.[58]

In the COMMAND-2 study, the effectiveness of the use of daclatasvir with PEG-IFN and RBV was evaluated in 71 treatment-naïve, noncirrhotic patients with HCV genotype 2.[59] Of the patients who received a shorter duration of therapy (12 or 16 weeks), 83% achieved SVR, whereas 62% achieved SVR in the PEG-IFN/RBV treatment group.[59] In addition, daclatasvir was evaluated in combination with sofosbuvir, with or without RBV, in 26 treatment-naïve HCV genotype 2 patients.[44] The study found that 96% of the patients achieved SVR, and there was no clear benefit of the use of RBV. However, the sample size was too small to allow the authors to draw firm conclusions.

HCV GENOTYPE 3

In the FISSION study, the effectiveness of treatment with sofosbuvir and RBV was evaluated in treatment-naïve patients. The study participants (n = 359) were randomly assigned to 24 weeks of treatment with PEG-IFN/RBV or

sofosbuvir/RBV for 12 weeks. Of the study participants, 20% had liver cirrhosis. The SVR rate of the PEG-IFN/RBV-treated group was higher than that of the sofosbuvir/RBV-treated group (63% vs 56%), but the difference was not statistically significant.[36] Due to the negative result from the FISSION study, the VALENCE study was performed to assess the efficacy of treatment with sofosbuvir and RBV for 24 weeks in treatment-naïve patients.[55] The SVR rate after 24 weeks of treatment was 94%, and there was no significant difference in the SVR rate between cirrhotic and noncirrhotic patients (92% vs 95%). Treatment with sofosbuvir and RBV for 24 weeks was evaluated in 145 treatment-experienced patients.[55] The SVR rate was 87% in the noncirrhotic group and 62% in the cirrhotic group. Therefore, alternative therapeutic options are required in treatment-experienced cirrhotic patients with HCV genotype 3.

Treatment with PEG-IFN, sofosbuvir, and RBV for 12 weeks was evaluated in treatment-experienced patients with HCV genotype 3. The SVR rate was 83% in the cirrhotic and noncirrhotic patients.[57] In the ELECTRON-2 study, the effectiveness of treatment with sofosbuvir and ledispavir was evaluated in patients with HCV genotype 3.[60] Of the 101 patients in the study, 51 treatment-naïve patients were randomly assigned to groups that received 12 weeks of sofosbuvir and ledispavir with or without RBV, whereas 50 treatment-experienced patients received 12 weeks of sofosbuvir/ledispavir with RBV. In the treatment-naïve patients, the SVR rate was 64% in the sofosbuvir/ledispavir-treated group and 100% in the group that received sofosbuvir/ledispavir with RBV. Among the treatment-experienced patients, the overall SVR rate was 82%, but treatment-experienced cirrhotic patients had the lowest SVR (73%). This result suggested that treatment using sofosbuvir/ledispavir with RBV is not recommended in treatment-experienced cirrhotic patients with HCV genotype 3.

The effectiveness of the use of daclatasvir in combination with sofosbuvir in treatment-naïve, noncirrhotic HCV genotype 3 patients has been evaluated. In this study, 18 participants were randomly assigned to groups that received 24 weeks of daclatasvir and sofosbuvir with or without RBV.[40] The SVR rate for sofosbuvir/daclatasvir was 89%. In the ALLY-3 study, the effectiveness of 12-week regimen of daclatasvir and sofosbuvir was evaluated in 101 treatment-naïve patients and 51 treatment-experienced patients, of which 21% had liver cirrhosis.[61] The SVR rate in the treatment-naïve patients was slightly higher than that of the treatment-experienced patients (91% vs 86%), but the result was not statistically significant. In contrast, the SVR rate in the noncirrhotic group was significantly higher than that of the cirrhotic group (94% vs 70%).[61] The ALLY-3 study did not explore the addition of RBV or extension of the duration of daclatasvir and sofosbuvir treatment in cirrhotic patients. Therefore, it is unknown whether the addition of RBV and increased treatment duration could improve SVR in treatment-experienced (failed sofosbuvir) cirrhotic patients. This regimen should be proposed as a therapeutic option in treatment-experienced cirrhotic patients in whom treatment with sofosbuvir and RBV had previously failed.[62]

HCV GENOTYPE 4

Previously, PEG-IFN and RBV therapy was the standard of care for patients with HCV genotype 4. However, PEG-IFN/RBV dual therapy has a poor sustained virologic response rate (SVR) (40%–60%).[63] On the other hand, PEG-IFN, sofosbuvir and RBV had an excellent SVR rate (96%).[36] In the NEUTRINO study, 28 treatment-naive patients received PEG-IFN, sofosbuvir, and RBV for 12 weeks, and the SVR rate was 96%. Only one patient did not achieve SVR, and this patient had liver cirrhosis. The side effect profile was similar to that associated with PEG-IFN and RBV therapy.[36] Similarly, in the COMMAND-1 study, the SVR rate was 100% among 12 patients who were treated with daclatasvir, PEG-IFN, and RBV for 24 weeks.[64] However, in a larger group of 82 treatment-naïve patients who were treated with daclatasvir-based therapy, patients received 24 weeks of daclatasvir-based triple therapy if extended rapid virologic response was achieved (HCV RNA less than the LLOQ at weeks 4 and 12). Otherwise, an additional 24 weeks of PEG-IFN and RBV was applied. The SVR rate was 78%, without a clear benefit in the absence of cirrhosis and the presence of CC-IL28B. The side effects profile was similar to that associated PEG-IFN and RBV treatment.[65] In addition, the effectiveness of the use of daclatasvir in combination with beclabuvir (75 mg or 150 mg) and asunaprevir for 12 weeks in treatment-naïve, noncirrhotic patients with HCV genotype 4 was evaluated.[66] In this pilot study ($n = 21$), the SVR rate was 90%.

In the RESTORE study, treatment with simeprevir, PEG-IFN, and RBV was evaluated in 35 treatment-naïve patients and 72 treatment-experienced patients with HCV genotype 4.[67] All patients received 12 weeks of triple therapy, followed by 12 or 36 weeks of PEG-IFN and RBV. A response-guided therapy approach (an additional 12 weeks of PEG-IFN and RBV dual therapy if HCV RNA was <25 IU/mL at week 4 and undetectable at week 12; otherwise, an additional 36 weeks) was applied in treatment-naïve and relapsed patients, whereas other patients received 36 weeks of dual therapy (total of 48 weeks). The SVR rate was 88% in the treatment-naïve patients and 86% in the relapsed patients. However, the SVR rate was lower in the partial responders (60%) and null responders (40%). Based on this result, simeprevir-based therapy was not recommended for patients with HCV genotype 4 who were null responders to previous therapy.

In the PEARL-1 study, the safety and efficacy of an oral, IFN-free regimen of ombitasvir (an NS5A inhibitor) and ABT-450 plus ritonavir (ABT-450/r) with/without RBV for 12 weeks were assessed in treatment-naïve and treatment-experienced noncirrhotic patients with HCV genotype 4.[68] The SVR rate was 100% in patients that received the combination therapy with RBV. However, the SVR was lower in the RBV-free treatment group, suggesting that RBV should be included in the therapy regimen. The most common side effects were fatigue, headache, and nausea. One patient had a grade 3 liver function test elevation (AST >5 × ULN), which was asymptomatic and resolved during continued dosing. None of the patients discontinued therapy due to side effects.

Sofosbuvir and RBV were evaluated among 103 Egyptian patients with HCV genotype 4. The participants were randomly assigned to 12 or 24 weeks of therapy. Of the study participants, 52% were treatment-experienced and up to 20% had compensated cirrhosis. Among the treatment-naïve, non-cirrhotic patients, the SVR rate was similar after 12 and 24 weeks of treatment (86% vs 90%). However, patients with cirrhosis will benefit from prolonged therapy, because the SVR rate was 67% in the group treated for 12 weeks, as against 100% in the group treated for 24 weeks, but this result was based on only six patients. Among the treatment-experienced patients, the SVR rate after the 24-week regimen was higher than the SVR after the 12-week regimen (89% vs 70%). Therefore, a 24-week treatment with sofosbuvir and RBV is recommended in treatment-experienced patients with HCV genotype 4. However, the SVR rate was lower in treatment experienced-cirrhotic patients: 60% in the 12-week treatment group and 67% in the 24-week treatment group.[69]

Sofosbuvir and ledipasvir were evaluated in patients with HCV genotype 4.[70] A small group of 21 patients (38% treatment-experienced; 40% with cirrhosis) received 12 weeks of sofosbuvir and ledipasvir. The SVR rate was 95% and no patient discontinued treatment. Based on this result, sofosbuvir and ledipasvir were recommended for management of patients with HCV genotype 4.[71]

Combinations of sofosbuvir with simeprevir or daclatasvir, with or without ribavirin, appear to be very attractive options for managing patients with HCV genotype 4; however, there is a lack of data to support the use of these combinations in these patients. Nevertheless, the European Association for the Study of the Liver (EASL) has included these treatment regimens as therapeutic options for the management of patients with HCV genotype 4.[18]

Grazoprevir and elbasvir were evaluated in HCV genotype 4 patients. 26 patients were treated with grazoprevir and elbasvir for 12 weeks.[72] All patients achieved SVR. Based on this result, the US FDA approved this regimen in patients with HCV genotype 4. However, a larger study is required to assess the safety and efficacy of this regimen in patients with HCV genotype 4. Summary of clinical trial data in HCV genotype 4 patients is listed in Table 2.

HCV GENOTYPES 5 AND 6

In the NEUTRINO study, six patients with HCV genotype 6 and one patient with HCV genotype 1 were treated with sofosbuvir, PEG-IFN, and RBV for 12 weeks.[36] All patients achieved SVR, and the side effect profiles were similar to those of therapy with PEG-IFN and RBV.

In the ELECTRON-2 study, 25 treatment-naïve patients with HCV genotype 6 were treated with sofosbuvir and ledipasvir for 12 weeks.[60] Only two (8%) of the patients in the study had liver cirrhosis. The SVR rate was 96% and no patient discounted therapy due to side effects.

In vitro, sofosbuvir and ledipasvir were efficacious in patients with HCV genotype 5. However, a clinical trial had not

Table 2: Summary of clinical trial data in HCV genotype 4 patients

Study (reference)	*n*	Treatment	Duration	SVR (%)	Limitations
Neutrino[36]	28	PEG-IFN, sofosbuvir and RBV	12 weeks	96	Small sample size and the study did not include patients who were treatment-experienced
COMMAND-1[63]	12	PEG-IFN, daclatasvir and RBV	24 weeks	100	Small sample size
COMMAND 4[65]	124	PEG-IFN, daclatasvir and RBV	24-48 weeks	78	Suboptimal response and longer duration of therapy is required
Hassanein *et al*[66]	21	Daclatasvir, beclabuvir and asunaprevir	12 weeks	90	Small sample size and patients who are difficult to treat were not included in the study
RESTORE[64]	107	PEG-IFN, simeprevir and RBV	24-48 weeks	40-88	Suboptimal response and longer duration of therapy is required
PEARL-1[67]	126	Ombitasvir and paritaprevi plus ritonavir with/without RBV	12 weeks	91-100	Patients with liver cirrhosis were excluded from the study and suboptimal response in the group who did not receive RBV
Esmat *et al*[68]	103	Sofosbuvir and RBV	12-24 weeks	100-60	Suboptimal response in the treatment experienced-group
Zeuzem *et al*[71]	26	Grazoprevir and elbasvir	12 weeks	100	Small sample size
Kapor *et al*[69]	21	Sofosbuvir and ledispavir	12 weeks	95	Small sample size

HCV: Hepatitis C virus, SVR: Sustained virologic response rate, RBV: Ribavirin, PEG-IFN: Pegylated interferon

been performed using sofosbuvir and ledipasvir. Therefore, the combination of sofosbuvir and ledipasvir cannot be recommended in patients with HCV genotype 5.[73]

CONCLUSIONS

DAAs are very effective and well tolerated by patients with HCV. Due to major advances in the field of HCV treatment, multiple IFN-free regimens are available to patients, which show an SVR rate greater than 90%, even among patients who are difficult to treat, such as treatment-experienced patients with cirrhosis.

Oral DAA regimens are well tolerated with negligible side effects, and most DAA regimens are pangenotypic; however, such therapies are quite expensive, but market competition may ease cost constraints in the coming years, allowing more patients to utilize DAA therapy.

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Conflicts of interest
There are no conflicts of interest.

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