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Next-Generation Direct-Acting Antiviral Drug-Based Regimens for Hepatitis C

Isaac Ruiz[1,2] · **Stéphane Chevaliez**[1,3,4] · **Jean-Michel Pawlotsky**[1,3,4]

Abstract
Purpose of Review This article reviews the most recent results of clinical trials supporting the approval and use of the so-called next-generation hepatitis C virus (HCV) direct-acting antiviral (DAA) drug regimens, including glecaprevir/pibrentasvir, sofosbuvir/velpatasvir/voxilaprevir, uprifosbuvir/grazoprevir/ruzasvir, and AL-335/simeprevir/odalasvir.
Recent Findings From 2014 and onwards, HCV DAA drugs belonging to four classes were approved in Europe and the USA. These combinations are generally safe and well tolerated and yield high rates of sustained virological response (>95%) in most patient populations. However, there is a need for treatment simplification and efficacy in difficult-to-cure patient populations. Phase II and III clinical trial data showed that glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir have pangenotypic activity and high efficacy across most patient populations. Uprifosbuvir/grazoprevir/ruzasvir and AL-335/simeprevir/odalasvir are at earlier stages of clinical development but look promising.
Summary The so-called next-generation HCV DAA combination regimens will soon be available and promise to be easy-to-use, highly efficient, pangenotypic, once-daily, all-oral, interferon- and ribavirin-free.

Keywords Hepatitis C virus · Direct-acting antiviral drugs · Next-generation regimens · Resistance-associated substitutions

This article is part of the Topical Collection on *Hepatitis C*

✉ Jean-Michel Pawlotsky
jean-michel.pawlotsky@aphp.fr

[1] INSERM U955, Créteil, France

[2] Department of Hepatology and Gastroenterology, Hôpital Henri Mondor, Université Paris-Est, Créteil, France

[3] National Reference Center for Viral Hepatitis B, C and D, Hôpital Henri Mondor, Créteil, France

[4] Department of Virology, Hôpital Henri Mondor, Université Paris-Est, 51 avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France

Introduction

Hepatitis C virus (HCV) infection represents a major public health problem, with over 71 million persons chronically infected worldwide [1•]. The primary goal of HCV therapy is to cure the infection, in order to prevent the complications of HCV-related hepatic and extra-hepatic disorders [2••]. The endpoint of therapy, the sustained virological response (SVR), is defined as an undetectable HCV RNA in a sensitive assay (limit of detection of the assay <15 international units [IU]/mL) 12 weeks (SVR12) or 24 weeks (SVR24) after the end of treatment [3].

Since the discovery of HCV in 1989, an important effort has been pursued to develop potent and well-tolerated antiviral therapies. Until 2011, the approved treatment was a combination of pegylated interferon (pegIFN)-α and ribavirin (RBV), administered for 24 or 48 weeks. With this regimen, the global rate of infection cure was roughly 50%, with frequent, sometimes serious adverse events and adherence issues. In 2011, the cure rates with pegIFN-α and RBV therapy were increased to approximately 70% in patients with genotype 1 infection through the addition of a first-wave, first-generation direct-acting antiviral (DAA) drug belonging to the nonstructural (NS) 3-4A protease inhibitor family (e.g., telaprevir or boceprevir). However, these combinations were poorly tolerated, especially in patients with advanced liver disease. They were rapidly abandoned in Europe and in the USA where patients were warehoused until safer DAA-based

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regimens became available. In 2014, 2015, and 2016, several drugs belonging to four DAA families were successively approved, either as standalone drugs or as fixed-dose, single-pill combinations. The four classes of HCV DAAs currently available include NS3-4A protease inhibitors, NS5A inhibitors, nucleotide analogue inhibitors of the HCV RNA-dependent RNA polymerase (RdRp), and non-nucleoside inhibitors of the RdRp [2••].

HCV regimens recommended by international society guidelines [2••, 4••] generally use an NS5A inhibitor as backbone, in combination with one or two other DAAs: indeed, the NS5A inhibitor daclatasvir can be combined with the nucleotide analogue sofosbuvir, whereas ledipasvir/sofosbuvir and velpatasvir/sofosbuvir are available as fixed-dose, single-pill combinations; the NS5A inhibitor ombitasvir is available as a fixed-dose, single-pill combination with the ritonavir-boosted protease inhibitor paritaprevir and can be used in combination with (genotype 1) or without (genotype 4) the non-nucleoside RdRp inhibitor dasabuvir; finally, the NS5A inhibitor elbasvir is available in a fixed-dose, single-pill combination with the second-generation protease inhibitor grazoprevir. The only NS5A-free combination includes sofosbuvir and the second-wave, first-generation protease inhibitor simeprevir.

These approved DAA-based combination regimens are generally well-tolerated and yield high SVR rates in most patient groups. However, the choice of treatment and its duration must be tailored to a number of parameters, including the HCV genotype/subtype, the severity of liver disease, and prior exposure to anti-HCV therapy. The need for treatment simplification makes it necessary that easy-to-use, highly efficient, pangenotypic, once-daily, all-oral, IFN- and RBV-free regimens be available in the near future.

Several next-generation compounds bearing pangenotypic antiviral activity and an improved barrier to resistance as compared to currently available drugs have reached late clinical developmental phases. They include NS5A inhibitors (pibrentasvir, ruzasvir, and odalasvir), NS3-4A protease inhibitors (glecaprevir and voxilaprevir), and nucleotide analogue inhibitors of the HCV RdRp (uprifosbuvir and AL-335). These compounds will be available as components of four fixed-dose, single-pill combinations, including glecaprevir/pibrentasvir, sofosbuvir/velpatasvir/voxilaprevir, uprifosbuvir/grazoprevir/ruzasvir, and AL-335/simeprevir/odalasvir, that may be approved in 2017 and 2018 (Table 1).

Here, we review the most recent results of clinical trials supporting the approval and use of these "next-generation" HCV DAA regimens based on these new compounds. These regimens will be available for patients with chronic HCV infection related to genotypes 1 to 6, with or without compensated cirrhosis. Because all of them contain a protease inhibitor, they should not be used in patients with decompensated liver disease, because of the risk of adverse events related to the high circulating protease inhibitor concentrations.

Glecaprevir/Pibrentasvir

Glecaprevir, a second-generation NS3-4A protease inhibitor, and pibrentasvir, a second-generation NS5A inhibitor, are co-formulated and dosed once daily as three 100 mg/40 mg pills, for a total dose of 300 mg/120 mg. Several phase II and III clinical trials have been presented or published in various patient populations.

Non-cirrhotic Patients Infected with HCV Genotypes 1 to 6

The ENDURANCE trials are phase III, randomized, open-label, multicenter studies evaluating the safety and efficacy of various durations of glecaprevir/pibrentasvir (G/P) treatment in non-cirrhotic patients infected with HCV genotypes 1 to 6 who were treatment-naïve or had been previously treated.

In ENDURANCE-1, 703 non-cirrhotic patients with chronic HCV genotype 1 infection, including 85% with a METAVIR score F0-F1 and 5% with HIV-1 coinfection, were treated with G/P for 8 or 12 weeks. Among them, 62% were treatment-naïve and 38% treatment-experienced (pegIFN with RBV, sofosbuvir plus RBV or the three drugs together). The SVR12 rates were 99.0% (348/351) and 99.7% (351/352) in patients treated for 8 and 12 weeks, respectively. There was only one virological breakthrough in the group of patients treated for 8 weeks. There was no effect on the outcome of therapy of the severity of liver disease, prior therapy, the presence of baseline resistance-associated substitutions (RAS) or HIV coinfection [5•].

ENDURANCE-2 included 202 non-cirrhotic patients infected with genotype 2 treated with G/P for 12 weeks; 29% were treatment-experienced (pegIFN or sofosbuvir plus RBV), and 20% had a METAVIR fibrosis score F2 or F3. The intent-to-treat SVR12 rate was 99% (195/196; no virological failure) [6•].

In ENDURANCE-3, 8 and 12 weeks of treatment with G/P were compared with 12 weeks of the combination of sofosbuvir and daclatasvir in 505 non-cirrhotic, treatment-naïve patients infected with HCV genotype 3. The intent-to-treat SVR12 rates were 95% (149/157; one virological breakthrough and five relapses) after 8 weeks of G/P, 95% (222/233; one virological breakthrough and three relapses) after 12 weeks of G/P, and 97% (111/115; one relapse) after 12 weeks of sofosbuvir and daclatasvir [7•].

Finally, in ENDURANCE-4, non-cirrhotic treatment-naïve and treatment-experienced patients infected with HCV genotypes 4 to 6 were treated with G/P for 12 weeks. The intent-to-treat SVR12 rates were 99% (75/76), 100% (26/266), and 100% (19/19) in patients infected with HCV genotypes 4, 5, and 6, respectively. One genotype 4 patient stopped treatment after 12 days but there were no virological failures [8].

Table 1 Next-generation DAA-based regimens for hepatitis C

Regimen	Drug class				Manufacturer	Dose	Dosage	Genotype indication
	Nucleotide analogue	NS3-4A protease inhibitor	NS5A inhibitor	Non-nucleoside RdRp inhibitor				
Currently approved regimens (first half of 2017)								
Sofosbuvir/ledipasvir	Sofosbuvir	–	Ledipasvir	–	Gilead	400 mg/90 mg	1 tablet once per day	1, 4, 5, 6
Sofosbuvir/velpatasvir	Sofosbuvir	–	Velpatasvir	–	Gilead	400 mg/100 mg	1 tablet once per day	1, 2, 3, 4, 5, 6
Sofosbuvir + daclatasvir	Sofosbuvir	–	Daclatasvir	–	Gilead/BMS	400 mg + 60 or 30 mg	1 tablet once daily + 1 tablet once daily	1, 2, 3, 4, 5, 6
Ombitasvir/paritaprevir/ritonavir + dasabuvir	–	Paritaprevir	Ombitasvir	Dasabuvir	AbbVie	12.5 mg/75 mg/50 mg + 250 mg	2 tablets once per day + 1 tablet twice per day	1
Ombitasvir/paritaprevir/ritonavir	–	Paritaprevir	Ombitasvir	–	AbbVie	12.5 mg/75 mg/50 mg	2 tablets once per day	4
Grazoprevir/elbasvir	–	Grazoprevir	Elbasvir	–	Merck	100 mg/50 mg	1 tablet once per day	1, 4
Sofosbuvir + simeprevir	Sofosbuvir	Simeprevir	–	–	Gilead/Janssen	150 mg	1 tablet once daily +1 tablet once daily	1, 4
Next-generation regimens								
Glecaprevir/pibrentasvir (G/P)	–	Glecaprevir	Pibrentasvir		AbbVie	100 mg/40 mg	3 tablets once per day	1, 2, 3, 4, 5, 6
Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX)	Sofosbuvir	Voxilaprevir	Velpatasvir		Gilead	400 mg/100 mg/100 mg	1 tablet once per day	1, 2, 3, 4, 5, 6
Uprifosbuvir/grazoprevir/ruzasvir (MK3)	Uprifosbuvir	Grazoprevir	Ruzasvir		Merck	225 mg/50 mg/30 mg	2 tablets once per day	1, 2, 3, 4, 5, 6
AL-335/simeprevir/odalasvir	AL-335	Simeprevir	Odalasvir		Janssen	400–800 mg/75–100 mg/25–50 mg	1 tablet once per day	1, 2, 3, 4, 5, 6

EXPEDITION-2 is another phase III study performed in HIV-coinfected patients without cirrhosis infected with HCV genotypes 1 to 4 or 6 treated with G/P for 8 weeks. The SVR12 rate was 100% (136/136) in this study, indicating similarly high efficacy in HIV-coinfected and in HCV-monoinfected patients [9].

Two phase III studies, CERTAIN-1 and CERTAIN-2, were conducted in non-cirrhotic Japanese patients infected with HCV genotypes 1 and 2, respectively. In genotype 1-infected patients, the SVR12 rate was 99% (128/129; no virological failure) after 8 weeks of G/P vs 100% (52/52) in patients who received ritonavir-boosted paritaprevir and ombitasvir without dasabuvir (control arm) [10]. In patients infected with genotype 2, the SVR12 rate was 98% (88/90; no virological failure) after 8 weeks of G/P vs 94% (43/46; two relapses) after 12 weeks of sofosbuvir plus ribavirin (control arm) [11].

Figure 1 shows the efficacy results from an integrated analysis of 1904 non-cirrhotic, treatment-naïve or treatment-experienced, NS3 and NS5A inhibitor-naïve patients with genotype 1 to 6 infection included in phase II and III clinical trials who received 8 or 12 weeks of the G/P combination [12]. Overall, G/P treatment was safe and well tolerated. The most frequent side effects were fatigue and headache, and serious adverse events occurred in less than 1% of patients. No significant laboratory abnormalities were reported.

Patients with Compensated Cirrhosis Infected with HCV Genotypes 1 to 6

EXPEDITION-1 is a phase III clinical trial including 146 patients with compensated cirrhosis infected with HCV genotypes 1, 2, 4, 5, and 6. The overall SVR12 rate was 99% (145/146). One patient infected with genotype 1a relapsed (genotype 1a SVR rate: 99%, 89/90). All patients infected with genotypes 2, 4, 5, and 6 achieved SVR [13••]. In EXPEDITION-2, a phase III trial evaluating 12 weeks of G/P treatment in HIV-coinfected patients with compensated cirrhosis infected with HCV genotypes 1 to 4, SVR12 was achieved in 14 patients out of 16; one patient with genotype 3 infection relapsed and one patient was lost to follow-up [9]. In the CERTAIN-1 and CERTAIN-2 studies performed in compensated cirrhotic patients in Japan, 12 weeks of the G/P combination yielded SVR rates of 100% (38/38) and 100% (18/18) in those infected with genotype 1 and 2, respectively [10, 11].

Patients infected with genotype 3 with compensated cirrhosis were not included in EXPEDITION-1. Thus, only phase II data are available in this population thus far. In the SURVEYOR-I study, treatment-naïve cirrhotics with genotype 3 infection were treated for 12 weeks, while treatment-experienced patients received G/P together with ribavirin for 12 weeks or without ribavirin for 16 weeks. The SVR12 rate was 96% (27/28; one relapse) in patients treated without ribavirin, and 100% (27/27) in those receiving ribavirin [14]. In SURVEYOR-II, genotype 3-infected treatment-naïve and treatment-experienced patients with cirrhosis were treated with 12 or 16 weeks of G/P, respectively. The SVR12 rates were 98% (39/40; no virological failure) in treatment-naïve patients receiving G/P for 12 weeks vs 96% (45/47; one virological breakthrough and one relapse) in treatment-experienced patients treated for 16 weeks. NS5A RASs were present in patients with virological failures [15].

Special Populations

EXPEDITION-4 is a phase III trial in genotype 1 to 6-infected, treatment-naïve, and treatment-experienced patients with or without cirrhosis, with chronic kidney disease stage 4 or 5. SVR12 was achieved by 98% of patients (102/104). No virological failures occurred. The G/P combination was well-tolerated with a favorable safety profile in this population [16].

G/P was also administered to liver and transplant recipients in the MAGELLAN-2 trial. They achieved SVR12 in

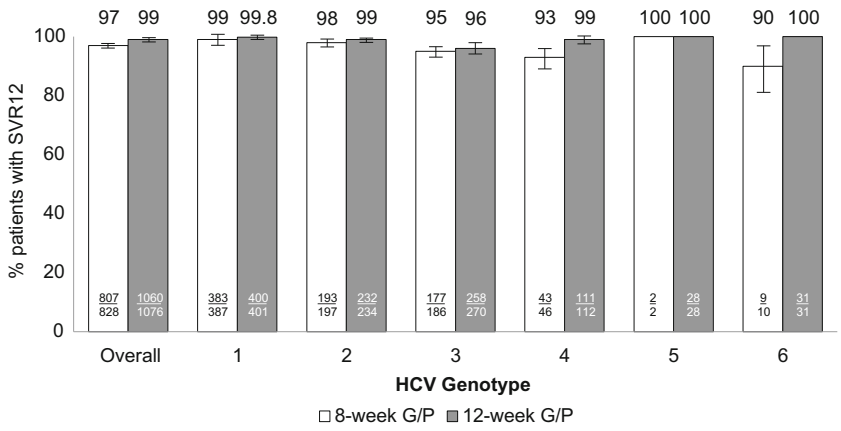

Fig. 1 SVR12 from an integrated analysis of 1904 non-cirrhotic, treatment-naïve or treatment-experienced, NS3 protease and NS5A inhibitor-naïve patients included in phase II and III clinical trials with 8 or 12 weeks of glecaprevir/pibrentasvir [12]

98% of cases (98/100), with one patient who relapsed post-therapy [17].

Retreatment of DAA-Exposed Patients

In the MAGELLAN-1, part 2 study, patients infected with genotype 1 or 4 and previously exposed to DAAs, including NS3-4A protease and/or NS5A inhibitors, were retreated with 12 or 16 weeks of G/P, without ribavirin. In the 12-week arm, SVR was achieved by 100% (14/14), 88% (14/16; one virological breakthrough and one relapse), and 79% (11/14; three relapses) of patients previously exposed to protease inhibitors only, NS5A inhibitors only, or both classes, respectively. In the 16-week arm, SVR was achieved by 100% (13/13), 94% (17/18; one virological breakthrough), and 81% (13/16; three virological breakthroughs) of patients exposed to protease inhibitors only, NS5A inhibitors only, or both classes, respectively. Virological failures occurred exclusively in patients harboring NS5A RASs at retreatment baseline [18•].

Virological Failures and Resistance to G/P

A pooled analysis of 2256 patients included in phase II and III G/P trials showed 22 virological failures (incidence 0.97%). The virological failure rates were 0.2% (2/889), 0.4% (2/466), 2.8% (18/643), and 0% (0/258) in patients infected with genotypes 1, 2, 3, and 4–6, respectively. There was no impact on SVR of the presence of baseline RASs in the NS3 protease or NS5A regions in patients infected with genotypes 1 and 2. Four genotype 3-infected patients who experienced virological failure had NS3 protease RASs A166S or Q168R at baseline, whereas 14 patients who experienced virological failure had NS5A RASs A30K, V31M, or Y93H at baseline [19].

Sofosbuvir/Velpatasvir/Voxilaprevir

Sofosbuvir, a nucleotide analogue inhibitor of the HCV RdRp, velpatasvir, a second-wave, first-generation NS5A inhibitor, and voxilaprevir, a second-generation NS3-4A protease inhibitor, are co-formulated and dosed once daily as 400 mg/100 mg/100 mg pills. Several phase II and III clinical trials have been presented or published in various patient populations.

Treatment-Naïve and Pegylated IFN/RBV-Experienced Patients

The results of two phase III trials have been presented. In POLARIS-2, 501 patients infected with HCV genotypes 1 to 6 were treated with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) for 8 weeks and compared with 440 patients treated with sofosbuvir/velpatasvir (SOF/VEL) for 12 weeks. Eighteen percent of them had compensated cirrhosis. Overall, the SVR rates were 95% (476/501) in the patients receiving 8 weeks of SOF/VEL/VOX vs 98% (432/440) in those receiving 12 weeks of SOF/VEL. Although the difference between the two groups was modest, there were 21 relapses in the SOF/VEL/VOX 8 weeks group, vs only three relapses in the SOF/VEL 12 weeks group. Most relapses occurred in patients infected with HCV genotype 1a. Indeed, in genotype 1a patients, the SVR12 rates were 92% (155/169; 14 relapses) vs 99% (170/172; one relapse) in the SOF/VEL/VOX and SOF/VEL groups, respectively. For the other genotypes, the SVR12 rates were, respectively, as follows: genotype 1b, 97% (61/63; two relapses) vs 97% (57/59; one relapse); genotype 2, 97% (61/63; two relapses) vs 100% (53/53); genotype 3, 99% (91/92; no virological failures) vs 97% (86/89; no virological failures); genotype 4, 92% (58/63; two relapses) vs 98% (56/57; one relapse); genotype 5, 94% (17/18; one relapse, no patient received SOF/VEL); genotype 6, 100% (30/30) vs 100% (9/9). Relapse was not more frequent in cirrhotics than in non-cirrhotic patients receiving the 8-week triple regimen. The presence of NS3 protease or NS5A RASs at baseline had a modest impact on the virological response [20•].

Only genotype 3-infected patients with compensated cirrhosis were included in the POLARIS-3 phase III trial. Approximately a third of them were pegIFN and RBV experienced. SVR12 was achieved in 96% of cases (106/110; two relapses) after 8 weeks of SOF/VEL/VOX vs 96% of cases (105/109; one virological breakthrough, one relapse) after 12 weeks of SOF/VEL. Neither prior treatment experience nor the presence of RASs at baseline had any effect on the SVR [21•].

In these two trials, the SOF/VEL/VOX regimen was safe and well-tolerated. The most frequent adverse events were fatigue, headache, and nausea. Diarrhea was more frequent in patients receiving voxilaprevir.

Retreatment of DAA-Exposed Patients

Two phase III trials were conducted in patients previously exposed to DAAs who failed to achieve SVR with these regimens. POLARIS-1 included 263 patients infected with HCV genotypes 1 to 6 who failed an NS5A inhibitor-containing regimen (51% received ledipasvir, 27% daclatasvir, 11% ombitasvir, and 13% another NS5A inhibitor). They were retreated with SOF/VEL/VOX for 12 weeks. The overall SVR12 rate was 96% (253/263). SVR was achieved in 99% of non-cirrhotic patients (140/142; no virological failure) and in 93% of patients with compensated cirrhosis (93%; one virological breakthrough due to non-compliance and six relapses). The presence of NS5A RASs at retreatment baseline had no effect on the SVR (98 vs 96% in patients without and with RASs, respectively) [22••].

In POLARIS-4, DAA-experienced patients who never received NS5A inhibitors were randomized to be retreated with either SOF/VEL/VOX or SOF/VEL for 12 weeks. The SVR12 rates were 97% (177/182; one relapse) vs 90% (136/151; one virological breakthrough and 14 relapses) in these two groups, respectively. With 12 weeks of SOF/VEL/VOX, SVR was achieved in 98% (96/98) of non-cirrhotics and in 96% (81/84) of patients with compensated cirrhosis. The presence of RASs at retreatment baseline had no effect on the outcome of retreatment [22••].

Uprifosbuvir/Grazoprevir/Ruzasvir

Uprifosbuvir, a new nucleotide analogue inhibitor of the HCV RdRp, grazoprevir, a second-generation NS3-4A protease inhibitor, and ruzasvir, a second-generation NS5A inhibitor, are co-formulated and dosed once daily as two 225 mg/50 mg/30 mg pills for a total dose of 450 mg/100 mg/60 mg. Only phase II data have been presented with this combination thus far.

Treatment-Naïve and Pegylated IFN/RBV-Experienced Patients

The C-CREST study included patients infected with HCV genotypes 1 to 6 receiving 8 to 16 weeks of uprifosbuvir/grazoprevir/ruzasvir (known as the MK3 combination) with or without ribavirin. SVR12 was achieved in 93% (39/42; two relapses) vs 98% (47/48; no virological failure) of patients infected with genotype 1a after 8 and 12 weeks of MK3, respectively. In patients infected with genotype 1b, SVR was achieved in 98% (45/46; one relapse) vs 100% (40/40) of cases after 8 and 12 weeks of MK3, respectively. In genotype 2-infected patients treated for 8 weeks, SVR was achieved in 91% of cases without ribavirin (29/32; three relapses) and in 83% of cases with ribavirin (25/30; four relapses). Genotype 2-infected patients treated for 16 weeks without ribavirin achieved SVR in 100% of cases (26/26). In patients infected with HCV genotype 3, SVR12 was achieved in 94% (50/53; three relapses) and 98% (48/49; one relapse) of those treated for 8 weeks without or with ribavirin, respectively; 97% (76/78; two relapses) and 99% (79/80; one relapse) of those treated for 12 weeks without or with ribavirin, respectively; and 98% (48/49; one relapse) and 96% (24/25; one relapse) of those treated for 16 weeks without or with ribavirin, respectively. The presence of NS5A RASs at baseline had no effect on SVR in patients infected with genotype 1. There was a trend towards a lower response rate in patients infected with genotype 3 harboring the Y93H RAS at baseline [23•]. Patients infected with genotypes 4 and 6 achieved SVR in 100% of cases (7/7 after 8 weeks and 4/4 after 12 weeks of MK3, respectively) [24].

Table 2 Future possible indications of next-generation HCV DAA regimens

Regimen	Genotype	Cirrhosis status		Prior treatment			Decompensated cirrhosis	Severe chronic kidney disease
		Non-cirrhotic	Cirrhotic	DAA-naïve	DAA-exposed NS5A-naïve	NS5A-exposed		
G/P	All	Yes	Yes	Yes	Pending	No	No[a]	Yes
SOF/VEL/VOX	All	Yes	Yes	Yes	Yes	Yes	No[a]	No
MK3	All	Yes	Yes	Yes	Pending	Yes	No[a]	Pending
AL-335/SIM/ODR	All	Yes	Pending	Yes	Pending	Pending	No[a]	Pending

G/P glecaprevir/pibrentasvir, *SOF/VEL/VOX* sofosbuvir/velpatasvir/voxilaprevir, *MK3* uprifosbuvir/grazoprevir/ruzasvir, *AL-335/SIM/ODR* AL-335/simeprevir/odalasvir

[a] Protease inhibitors are not recommended in patients with Child-Pugh B cirrhosis and contraindicated in those with Child-Pugh C cirrhosis

The most common adverse events with the MK3 combination were fatigue, headache, and nausea. Adverse events were more frequent when ribavirin was used.

Retreatment of DAA-Exposed Patients

In the C-SURGE trial, 93 genotype 1-infected patients who failed to achieve SVR after an NS5A inhibitor-containing regimen were randomized to receive MK3 with ribavirin for 16 weeks or MK3 alone for 24 weeks. SVR12 was achieved in 98% (43/44) and 100% (49/49) of cases, respectively, without any virological failure [25].

AL-335/Odalasvir/Simeprevir

AL-335, a nucleotide analogue inhibitor of the HCV RdRp, simeprevir, an NS3-4A protease inhibitor, and odalasvir, an NS5A inhibitor, will be co-formulated and dosed once daily. Early phase II data have been presented with different dosages of this combination.

In treatment-naïve patients without cirrhosis (METAVIR score F0-F3) infected with HCV genotype 1, a 100% SVR rate was achieved after 6 and 8 weeks of AL-335 800 mg, odalasvir 50 mg, and simeprevir 75 mg (20/20 and 14/14, respectively). The SVR rate was also 100% (8/8) in patients treated for 8 weeks with AL-335 400 mg, odalasvir 50 mg, and simeprevir 100 mg. Among patients with genotype 3 infection treated with AL-335 800 mg, odalasvir 50 mg, and simeprevir 75 mg, five out of five patients relapsed after 8 weeks of therapy, whereas SVR was achieved in 77% of cases (10/13; one virological breakthrough, two relapses) after 12 weeks of the combination [26].

Conclusion

Two pangenotypic, next-generation DAA combination regimens will be approved in Europe and the USA in the middle of 2017. The G/P combination will find an indication as first-line therapy in treatment-naïve or pegIFN and RBV-experienced patients with chronic hepatitis C, including those with and without compensated cirrhosis. Eight weeks of G/P therapy yield high SVR rates in the vast majority of treatment-naïve, non-cirrhotic patients, while 12 weeks will be suited to the remaining patients. More data will be needed to determine whether G/P can also be used for retreatment of DAA-exposed patients. However, this combination does not appear to be optimal for patients previously exposed to NS5A inhibitors (Table 2).

The SOF/VEL/VOX triple combination regimen does not appear to yield higher SVR rates than SOF/VEL as first-line therapy, except in patients infected with genotype 3 who have cirrhosis and/or are treatment-experienced. In the latter group, voxilaprevir could help avoid using RBV in combination with sofosbuvir and velpatasvir. SOF/VEL/VOX may also be useful to shorten treatment duration to 8 weeks in some genotypes. Based on the POLARIS-1 and POLARIS-4 trials, SOF/VEL/VOX appears to be an excellent option for retreatment of patients previously exposed to DAAs, such as NS3-4A protease and NS5A inhibitors (Table 2).

Phase III data will help define the future use of the remaining two triplet combinations, including uprifosbuvir/grazoprevir/ruzasvir and AL-335/odalasvir/simeprevir. Ultimately, treatment of HCV infection will be pangenotypic, IFN- and ribavirin-free, with durations of 8 to 16 weeks. Remaining issues include patients infected with genotype 3, especially those with baseline NS5A RASs; patients who failed a prior DAA-based treatment, especially those exposed to an NS5A inhibitor who selected specific RASs; and patients with decompensated cirrhosis who will not benefit from the next-generation regimens because of the contraindication of protease inhibitors in this population.

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Compliance with Ethical Standards

Conflict of Interest Isaac Ruiz has served as an advisor for AbbVie.

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