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Pharmacokinetic and pharmacodynamic evaluation of daclatasvir, asunaprevir plus beclabuvir as a fixed-dose co-formulation for the treatment of hepatitis C

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Abstract

Introduction: Many reports have evaluated the clinical efficacy and safety of the fixed-dose all-oral combination of daclatasvir, asunaprevir and beclabuvir (DCV-TRIO), which was approved in Japan in December 2016 for the treatment of hepatitis C genotype 1 infection.

Areas covered: This article reviews the pharmacodynamic and pharmacokinetic properties of the DCV-TRIO combination. The topics covered include data regarding the drug's absorption, distribution, metabolism, excretion and antiviral activity strategies. Its therapeutic efficacy and safety in genotype 1 infection from phase 2/3 clinical trials are also discussed.

Expert Opinion: The ideal regimen for the treatment of HCV should be potent, pangenotypic, RBV-free, safe, co-formulated and affordable. Considering these characteristics, DCV-TRIO is neither pangenotypic nor potent enough against genotype 1a, regardless of the presence or absence of cirrhosis.

Other potential limitations of this regimen are its dosification (twice-daily), and the fact that since it includes a protease inhibitor, it is contraindicated in decompensated cirrhosis. For these reasons, it has only been approved in Japan, where more than 70% of the patients are infected with genotype 1b. However, this co-formulation might still have a place in the treatment of non-cirrhotic patients infected with genotype 1b provided that massive access to treatment is facilitated.

Keywords: asunaprevir; beclabuvir; daclatasvir; fixed-dose combinations; Hepatitis C; pharmacodynamics; pharmacokinetics.

LIST OF ABBREVIATIONS

AEs: Adverse events

ASV: Asunaprevir

AUC: Area under the concentration curve

BCRP: Breast cancer resistance protein

BCV: Beclabuvir

Cmin: Minimum observed plasma concentration at 12 hours post-dose

Cmax: Maximum observed plasma concentration

CYP: cytochrome P450

DAAs: Direct acting antivirals

DCV: Daclatasvir

IFN: Interferon

GT: Genotype

h: Hours

HCV: Hepatitis C virus

OATP: Organic anion-transporting polypeptide

OCT: Organic cation transporter

PegIFN: Pegylated Interferon

RAS: Resistance associated substitutions

RBV: Ribavirin

SVR: Sustained virological response

SVR12: Sustained virological response after 12 weeks of treatment

tmax: Time of maximum observed plasma concentration

t1/2: Half-life

1. INTRODUCTION

Hepatitis C virus infection (HCV) chronically infects 71 million people worldwide [1,2]. In anti-HCV treatment, the absence of viral load 12 or 24 weeks after therapy withdrawal is known as sustained virological response (SVR), which means that the infection is cured. The achievement of a SVR has the goal to prevent liver fibrosis progression and it is associated with a survival benefit in cirrhosis [3,4]. Therefore, SVR is the therapeutic aim of current anti-HCV therapies.

During the past 6 years, direct acting antivirals (DAAs) revolutionized HCV treatment. Fortunately, this life-threatening viral infection can now be cured in nearly all patients thanks to all-oral interferon (IFN)-free regimens that not only improve treatment safety and tolerability, but, most of all, increase SVR rates and expand access to cure to formerly IFN-contraindicated patients [3].

2. OVERVIEW OF THE MARKET

To address the limited effectiveness, long treatment duration and severe adverse events (AEs) of PegIFN/RBV, extensive efforts were directed toward the development of DAAs that target key steps of viral life cycle: the NS3/4A protease, the NS5A protein, and the NS5B polymerase [5,6].

Depending upon the HCV genotype (GT) and the patient characteristics, DAAs, such as simeprevir, sofosbuvir and daclatasvir (DCV), were used in various combinations, with or without PegIFNα and/or RBV [7]. Unfortunately, these regimens exhibited a significant increase of side effects and unacceptably low SVR rates in treatment-experienced cirrhotic patients [6,8].

Nowadays, IFN-free regimens of more potent and pangenotypic DAAs have the potential to achieve high SVR rates (over 95%) with shorter treatment durations, even in difficult-to-treat populations in the interferon era [3,9-12]. However, despite the overall high success of dual DAA combinations, challenges remain in certain patient populations [13,14]. For example, HCV GT-3 exhibit lower SVR rates, especially in cirrhotic patients [8,15]. In addition, quasispecies harboring resistance associated substitutions (RAS) and poor drug adherence may lead to impaired treatment responses [16,17]. Moreover, patients with advanced chronic kidney disease and those who failed a regimen containing a NS5A inhibitor are in need of new HCV therapies [14].

To address these issues, novel regimens were approved. Bristol-Myers Squibb released a triple-drug combination of DCV [18,19], asunaprevir (ASV) [20,21] and beclabuvir (BCV) [22], with and without RBV [23,24]. Afterwards, results using the glecaprevir/pibrentasvir co-formulation [25] and another consisting of sofosbuvir, velpatasvir, and voxilaprevir were reported [26]. The aim of this review is to resume the pharmacodynamic and pharmacokinetic characteristics of the fixed-dose co-formulation of DCV, ASV and BCV and its clinical implication.

3. DOSING ROUTES

The all-oral three-drug fixed-dose combination, consisting of 30mg DCV, 200mg ASV and 75mg BCV formulated as a single film-coated twice-daily tablet, exhibited high SVR rates after 12 weeks of treatment in GT-1-infected patients [27]. Box 1 summarizes the major characteristics of this co-formulation.

4. CHEMISTRY

DCV is a low molecular weight compound (738.89 g/mol) with an empirical formula of $C_{40}H_{50}N_8O_6$.

ASV is a low molecular weight compound (748.289 g/mol) with an empirical formula of $C_{35}H_{46}ClN_5O_9S$.

BCV is a low molecular weight compound (659.846 g/mol) with an empirical formula of $C_{36}H_{45}N_5O_5S$.

5. PHARMACODYNAMICS

DCV (formerly BMS-790052) is a first-in-class inhibitor of the NS5A phosphoprotein which binds within the first 100 amino acids of the amino terminus of the protein [28]. The initial rapidity with which DCV reduces HCV RNA in the serum, ~2 $\log_{10}$ reduction within 6 hours (h) of administration with a slower decline thereafter, suggests that it blocks virion assembly and release as well as viral RNA synthesis [29].

This drug exhibits a potent pangenotypic antiviral activity in vitro (GTs 1-6) [18,19,30], and displays additive or synergistic inhibitory activity in combination with PegIFNα/RBV, danoprevir, ASV or BCV [28,31].

ASV (formerly BMS-650032) is a potent second-generation, selective NS3 protease inhibitor which suppress the processing of HCV polyprotein to yield mature viral proteins, and the impairment of immune escape linked to the additional ATPase/helicase activity of NS3 harming the interferon signaling [32-35].

ASV showed high antiviral activity against GTs 1/4/5/6, and relatively weak antiviral activity against GTs 2/3 [21]. ASV exhibits additive or synergetic efficacy in combination with IFNα, RBV, DCV and/or BCV [20,36].

BCV (formerly BMS-791325) is an allosteric inhibitor of NS5B RNA-dependent RNA polymerase in a time-dependent manner [37], and thus prevents the formation of active replication complexes [38]. It is a thumb site 1-NS5B polymerase ligand which inhibits the initiation step of RNA replication [39] and not the elongation step. BCV has been shown to equally inhibit de novo and primer dependent synthesis more potently than previously studied compounds [40], thus resulting the most effective thumb site 1 inhibitor of GT-1 NS5B polymerase [37].

BCV inhibits recombinant NS5B proteins derived from GTs 1/3/4/5 and with variable activity against GT-6 and relatively weak antiviral activity against GT-2 [22,40]. BCV shows additive synergistic effects in combination with DCV, ASV, and human lambda 1 IFN [31,36].

6. PHARMACOKINETICS AND METABOLISM

Numerous in vitro and in vivo nonclinical pharmacokinetic studies evaluating the absorption, distribution, metabolism and excretion of DCV, ASV and BCV have been conducted (Table 1).

6.1. Daclatasvir

Oral DCV is readily absorbed, reaching peak plasma concentrations (Cmax) at a median time (tmax) of 1-2 h with a half-life (t1/2) of 12-15 h [41]. Approximately 99% of plasma DCV is bound to proteins, independently of dose [42].

DCV is a substrate of the P-glycoprotein efflux pump and the oral bioavailability is 67%. DCV is an inhibitor of P-glycoprotein, organic anion-transporting polypeptide (OATP) 1B1 and breast cancer resistance protein (BCRP) transporters [18,43]. DCV also inhibits renal

uptake transporters, OAT 1 and 3, and organic cation transporter (OCT) 2, but is unlikely to have a clinically significant effect on the transporter substrates [18].

DCV is metabolized by cytochrome P450 (CYP) 3A isoenzymes, predominantly CYP3A4 [18,43]. There are no metabolites present in the circulation at concentrations <5% of the parent drug concentration. More than 80% of the dose is excreted in the feces and 6.6% in urine [18].

6.2. Asunaprevir

Following single doses of ASV oral suspension, median tmax and t1/2 of ASV are similar in healthy and HCV-infected subjects ranging from 2 to 4 h and from 14 to 22 h, respectively [44].

The high oral clearance of ASV coupled with a potent antiviral activity suggest a strong preferential hepatic distribution [21,44]. The liver-to-plasma accumulation ratio is approximately 100:1. There is limited or no distribution of ASV in nervous, endocrine, reproductive and fatty tissues [21,45].

ASV is a substrate and a weak inducer of CYP3A4. The biotransformation of ASV is characterized by the production of many metabolites, mainly the products of oxidative metabolism. Additionally, the Cmin values for ASV do not appear to increase notably at higher doses with repeated administration, which is consistent with a compound inducing its own metabolism [44].

The elimination of ASV involves multiple pathways (biliary, metabolic and intestinal secretion) leading to excretion of ASV and its metabolites in the feces, with minimal elimination in urine [46].

6.3 Beclabuvir

BCV has an oral bioavailability of 66%, a plasma t1/2 of 8.3 h and a hepatotropic disposition (liver-to-plasma ratios ranging from 1.6- to 60-fold across species) [22,47].

Exposure to BCV in terms of Cmax and area under the concentration curve (AUC) are dose-dependent and more than dose proportional, accordingly with the expectation of once- or twice-daily dosing. Therefore, a satisfying antiviral response can be expected for repeated administration even at the lowest tested doses (100 mg) [48] while single doses above 300 mg provide little additional antiviral benefit.

BCV undergoes CYP3A4 metabolism and is metabolized to an equipotent compound (BMS-794712) which shows a similar pharmacokinetic profile, with a plasma exposure corresponding to 22% of the parent value, hence contributing significantly to the total antiviral activity [48]. It is excreted mainly in the feces.

6.3. Drug to drug interaction

The addition of BCV to DCV+ASV at two doses (75mg or 150mg) did not show any clinically meaningful interaction among treatment-naïve, non-cirrhotic, GT-1 infected patients [24,23,40,45]. However, as all of these drugs are CYP3A4 substrates, OATP1B1 and P-glycoprotein inhibitors, drug interactions prevent its co-administration with several drugs, which share the same metabolic pathways, such as rifampin, phenytoin, carbamazepine, etc.

6.4. Patients with renal impairment

Even though these drugs are primarily excreted in feces (renal excretion resulting <10%), their mean concentrations were higher in moderate and severe renal impairment than normal renal function.

A good tolerability profile was displayed by this combination in patients with renal impairment. Although patients with renal impairment do not require dose adjustment, those with severe renal disease not on hemodialysis treatment should receive DCV/ASV/BCV once daily [40,45].

7. CLINICAL EFFICACY: PHASE 2 AND 3 TRIALS

Previous studies with dual DCV+ASV therapy, with or without PegIFN+RBV demonstrated high SVR rates in GT-1b-infected patients who were treatment-naïve or null responders to prior IFN-based therapy or IFN-ineligibles or intolerants. However, a high rate of viral breakthrough occurred in patients infected with GT-1a [49-52].

In search of a more effective therapy, the addition of BCV to DCV+ASV was proposed as it ensures inhibition of 3 distinct viral targets responsible for HCV replication. Potentially, this strategy would reduce virologic failure, increase the SVR rate and protect against the emergence of viral resistance.

The open-label, randomized phase 2a study [23], evaluating the safety and efficacy of the combination of the single agents DCV (60mg, once daily), ASV (200mg, twice daily), and BCV (75 or 150mg, twice daily) interferon-/RBV-free for 12 or 24 weeks in treatment-naïve GT-1a or 1b-infected patients without cirrhosis, showed SVR rates up to 94% after 12 weeks, even among patients with reduced interferon responsiveness predicted by IL28B genotypes. No viral breakthrough or relapse was observed in patients treated with the 75mg twice-daily dose of BCV.

Data from a larger expansion cohort [24] confirmed that after 12 weeks of therapy with the three-drug combination, interferon-free with or without RBV, SVR was achieved by 90% of treatment-naïve GT-1-infected patients (83% GT-1a), including patients with advanced cirrhosis. Virological failures were infrequent and appeared unrelated to BCV dose or inclusion of RBV in the regimen.

Combining results from the pilot and expansion cohort gives that 12 weeks three-drug combination with the 75mg BCV dose is an effective and adequate treatment option, suggesting no advantage in terms of virological clearance by extending treatment duration to 24 weeks, and that RBV may be excluded from this DAA combination therapy without decrease in SVR rates. These results from phase 2 studies supported the evaluation of this regimen in large international phase 3 trials in GT-1 infected patients only treated with an oral twice-daily fixed-dose, single-tablet combination of DCV 30mg + ASV 200mg + BCV 75mg (the DCV-TRIO regimen). Table 2 summarizes the main results from phase 3 studies.

The first of these trials were conducted in North America, Canada, France and Australia, among non-cirrhotic (UNITY-1 study [53]) and cirrhotic (UNITY-2 study [54]; with or without RBV) GT-1-infected patients, and demonstrated similar high SVR rates after 12 weeks, with low rates of serious AEs and treatment discontinuations. Treatment-experienced and -naïve patients infected with HCV GT-1 without cirrhosis had SVR rates of 89% and 92%, respectively [53]. Otherwise, in patients with compensated cirrhosis, SVR was achieved by 87% and 93% of those who received the fixed-dose combination alone, and by 93 and 98% of those with RBV added to the regimen after 12 weeks of DCV-TRIO, respectively [54]. Most patients in these two studies were infected with GT-1a and had IL28B non-CC genotype (>70%). The response among GT-1b patients was higher

(≥96%) than among those infected with GT-1a in the treatment-experienced and the naïve cohorts, suggesting that the inclusion of RBV may be beneficial for GT-1a-infected patients.

In the UNITY-3 trial carried out in GT-1 Japanese patients (99% GT-1b) with or without compensated cirrhosis [55], 12 weeks of treatment with DCV-TRIO resulted in SVR rates of ≥96% in both treatment-naïve and IFN-experienced cohorts, compared with 87% in patients who received the RBV-free, combination of DCV+ASV (DUAL) therapy for 24 weeks, which is approved for treatment of GT-1 infection in Japan.

The UNITY-4 phase 3 clinical trial [56], conducted in South Korea, Taiwan, and Russia, evaluated the RBV-free, DCV-TRIO combination for 12 weeks in a population reflective of the distribution of patients seen in clinical practice in these countries, including treatment-naïve and -experienced patients with GT-1 infection, with and without compensated cirrhosis. Twelve weeks of DCV-TRIO provided 98.6% and 100% SVR in treatment-naïve and -experienced patients, respectively. The only two treatment-naïve patients who relapsed were both found to be infected with GT-6. Therefore, all patients with confirmed GT-1 infection achieved SVR, regardless of GT-1 subtype, prior treatment history or cirrhosis status.

In February 2017, an observational study to determine the real-world incidence proportion of hepatic toxicity and all adverse drug reactions has started in Japan following the marketing authorization for DCV-TRIO in this country [57].

8. SAFETY

In the phase 2 clinical trials [23,24] and UNITY studies [53-56], DCV-TRIO showed a high safety profile with minimal serious AEs and AE–related discontinuations, and no

difference regarding the dosage or duration of the therapy, generally similar in patients with or without cirrhosis. This tolerability profile is also similar to that of ASV+DCV [58,59], suggesting that the addition of BCV does not affect the safety profile of this combination.

The most common AEs (more than 10% by total) are headache, asthenia, fatigue and gastrointestinal complaints, which are mild or moderate in intensity. ALT elevations are the most common grade 3-4 laboratory abnormalities in the RBV-free DCV-TRIO regimen for 12 weeks, followed by grade 3 elevated AST. The addition of RBV to DCV+ASV+BCV was associated with more notable haemoglobin reductions from baseline compared with DCV-TRIO alone, but no grade 3/4 haematological events were reported or associated dose reductions warranted.

9. RESISTANCE

A recently published pooled resistance analysis of DCV-TRIO clinical data [60] showed that the addition of BCV to DCV+ASV produced high SVR rates after 12 weeks of treatment (SVR12) in GT-1b-infected patients with pre-existing NS5A RAS. This differs from DCV+ASV efficacy studies where high SVR12 rates were only observed in GT-1b patients without pre-existing NS5A RAS indicating that the inclusion of BCV to ASV+DCV increased the resistance barrier, overcoming the reduced drug susceptibility conferred by baseline NS5A RAS.

The prevalence of baseline NS5A RAS to DCV at positions 28, 30, 31, or 93 was roughly similar between GT-1a (12%) and GT-1b (16%), but with more NS5A-Y93 polymorphisms in GT-1b (13% vs 1%). All GT-1b-infected patients with baseline NS5A polymorphisms achieved SVR12, except three who failed the therapy with pre-treatment NS5A-L31 or Y93 [55]. Among GT-1a-infected patients, baseline NS5A-M28T, Q30, L31M, or Y93 reduced

the likelihood of achieving SVR12 by 35% in patients who received RBV and to 54% in patients treated without RBV. In contrast, pre-existing NS3 and NS5B RAS to ASV (R155K and D168) and BCV (P495) are less frequently observed at baseline in both GT-1a and GT-1b. There was no association between detection of baseline NS3-Q80K or NS5B-A421 and virologic outcome.

In the pooled DCV-TRIO resistance analysis study [60], RAS at NS3-R155K, NS5A-Q30 and NS5B-P495 were the most frequently detected at viral breakthrough in GT-1a-infected patients, although NS5B variants were no detected in patients experiencing relapse.

Most (89%) virologic failures in GT-1a were associated with dual- or triple-class resistance, with dual-class resistance mostly observed in relapsers and triple-class seen most often among patients with on-treatment virologic failure.

10. CONCLUSION

The pooled analysis of these phase 2 and 3 studies provides an overall picture of efficacy and safety of DCV-TRIO and reports high SVR rates in GT-1-infected patients treated for 12-weeks, irrespective of RBV use, prior IFN-based therapy, cirrhosis status, IL28B genotype, baseline resistance associated, or expansion of the duration of the treatment to 24 weeks.

11. REGULATORY AFFAIRS

Because of these results, DCV-TRIO has been launched and approved in Japan in December 2016 for the treatment of HCV GT-1 patients under the name Ximency as a fixed-dose three-drug combination treatment with twice daily dosing [61,62].

11. EXPERT OPINION

After several years of development and release of DAAs for the treatment of hepatitis C, it seems that the pipeline shrinked. The currently approved regimens are potent and safe, and therefore no new drugs are currently under development. Indeed, in the past meeting of the American Association for the Study of the Liver Diseases in October 2017 no new regimens were presented.

The ideal regimen for the treatment of hepatitis C should be potent, pangenotypic, RBV-free, safe, co-formulated and affordable. Taking into account these characteristics, DCV-TRIO fails not only because it is not pangenotypic, but also because it is not potent enough against GT-1a.

The UNITY trials [53-56] are large and well-designed studies in which 1078 HCV GT-1 patients with or without compensated cirrhosis who were treatment-naïve or experienced received DCV-TRIO. Overall these studies showed high SVR rates in non-cirrhotic patients infected with HCV GT-1b. In GT-1b patients with cirrhosis, the evidence is weaker since a total of 96 patients with these characteristics were included taking together the UNITY-2, UNITY-3 and UNITY-4 studies, reporting an overall SVR rate of 90 to 100% in patients treated without RBV [53,54,55]. In patients with GT-1a, SVR rates were unacceptably low, regardless of the presence or absence of cirrhosis.

Other potential limitation of DCV-TRIO is its dosification, which is every twelve hours and the fact that since it includes a protease inhibitor, it is contraindicated in decompensated cirrhosis.

For these reasons, this co-formulation has only been approved in Japan, where more than 70% of the patients are infected with HCV GT-1b [63]. A summary of all past and current DAA treatment options for HCV GT-1b infection is shown in Table 3.

An important issue when considering which antiviral regimens are available in a given country or region is related to costs. DCV-TRIO might still have a place in the treatment of non-cirrhotic GT-1b patients provided that massive access to treatment is facilitated through negotiations between pharmaceutical companies and treatment payers. If this is not the case, other potent regimens with activity against GT-1a and other genotypes, and with more available evidence from larger clinical trials and real-life studies are preferable.

In conclusion, DCV-TRIO´s role in the treatment of hepatitis C is currently very limited, and this regimen will most likely be out of the treatment options in the future.

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Box 1. Drug summary

Drugs	Co-formulation of daclatasvir, asunaprevir and beclabuvir
Chemical structure	$C_{40}H_{50}N_8O_6$ (DCV) $C_{35}H_{46}ClN_5O_9S$ (ASV) $C_{36}H_{45}N_5O_5S$ (BCV)
Phase	Approved
Mechanism of action	Specific inhibitors of viral NS5A (DCV), NS3 (ASV) and NS5B (BCV) enzymes/proteins
Indication	HCV infection
Route of administration	Oral (one pill twice-daily)
Pivotal trials	UNITY-1 [53], UNITY-2 [54], UNITY-3 [55] and UNITY-4 [56]
Registrational status	Approved by PMDA (Japan) on December 19th, 2016

Table 1. Main pharmacologic characteristics of the study drugs

	Daclatasvir	Asunaprevir	Beclabuvir
Viral target	NS5A	NS3	NS5B
Dosage	30 mg twice a day	200 mg twice a day	75 mg twice a day
Plasma t1/2	12-15 h	14-22 h	8.3 h
Cmax (ng/mL)	974–975 ng/mL	473–492 ng/mL	3141 ng/mL
Cmin (ng/mL)	336–356 ng/mL	13.4–15.5 ng/mL	309 ng/mL
AUCτ (h·ng/mL)	6960–7144 h·ng/mL	1272–1387 h·ng/mL	14,670 h·ng/mL
tmax	1-2 h	2-4h	2h
Plasma protein binding	99%	>99%	Unknown
Hepatic metabolism	CYP3A4	CYP3A4	CYP3A4
Transporter inhibitor	OATP1B1/3, P-glycoprotein	OATP1B1/3, P-glycoprotein	OATP1B1, P-glycoprotein
Elimination	Feces (88%), urine (6.6%)	Feces (84%), urine (<1%)	Feces, urine (<10%)

Table 2. Virologic response of twice-daily fixed-dose combination of DCV 30 mg; ASV 200 mg; and BCV 75 mg (DCV-TRIO) with or without ribavirin for 12 weeks from phase 3 clinical trials.

UNITY-1 STUDY Poordad *et al*. 2015	Total: 415 without cirrhosis	Treatment naïve: 312		Treatment experienced: 103	
	Treatment	DCV-TRIO		DCV-TRIO	
	SVR12, No. (%)	287 (92%)		92 (89.3%)	
	SVR12 in GT-1a, No./total No. (%)	206/229 (90%)		64/75 (85.3%)	
	SVR12 in GT-1b, No./total No. (%)	81/83 (97.6%)		28/28 (100%)	
	On-treatment failures: - Virologic breakthrough - No responders with missing or detectable HCV-RNA at end of treatment	6 3		2 2	
	Posttreatment failures: - Relapse - Other	15 1		6 1	
UNITY-2 STUDY Muir *et al.* 2015	Total: 202 (53% with cirrhosis)	Treatment naïve: 112		Treatment experienced: 90	
	Treatment	DCV-TRIO (n: 57)	DCV-TRIO + RBV (n: 55)	DCV-TRIO (n: 45)	DCV-TRIO + RBV (n: 45)
	SVR12, No. (%)	53 (93%)	54 (98.2%)	39 (86.7%)	42 (93.3%)
	SVR12 in GT-1a, No./total No. (%)	36/40 (90%)	38/39 (97.4%)	30/35 (85.7%)	32/35 (91.4%)
	SVR12 in GT-1b, No./total No. (%)	17/17 (100%)	15/15 (100%)	9/10 (90%)	10/10 (100%)
	On-treatment failures: - Virologic breakthrough - No responders with missing or detectable HCV-RNA at end of treatment	0 0	0 0	1 0	1 1
	Posttreatment failure: - Relapse - Other	4 0	0 1	5 0	1 0
UNITY-3 STUDY Toyota *et al.* 2016	Total: 217 (21% with cirrhosis)	Treatment naïve: 152		Treatment experienced: 65	
	Treatment	DCV-TRIO		DCV-TRIO	
	SVR12, No. (%)	146 (96%)		62 (95.4%)	
	SVR12 in GT-1a, No./total No. (%)	3/3 (100%)		0/1	
	SVR12 in GT-1b, No./total No. (%)	143/149 (96%)		62/64 (97%)	
	On-treatment failures: - Virologic breakthrough - No responders with missing or detectable HCV-RNA at end of treatment	0 5		0 1	
	Posttreatment failure:				

	- Relapse - Other	1 0	2 0
UNITY-4 STUDY Kao *et al.* 2016	Total: 169 (14% with cirrhosis)	Treatment naïve: 138	Treatment experienced: 31
	Treatment	DCV-TRIO	DCV-TRIO
	SVR12, No. (%)	136 (98.6%)	31 (100%)
	SVR12 in GT-1a, No./total No. (%)	6/6 (100%)	2/2 (100%)
	SVR12 in GT-1b, No./total No. (%)	128/128 (100%)	29/29 (100%)
	SVR12 in GT-6, No./total No. (%)	2/4 (50%)	/
	On-treatment failures: - Virologic breakthrough - No responders with missing or detectable HCV-RNA at end of treatment	 0 0	 0 0
	Posttreatment failure: - Relapse - Other	 2 with GT6 0	 0 0

Abbreviations: Genotype (GT); Sustained virological response after 12 weeks of treatment (SVR12).

Table 3. Summary of approved DAA regimens and SVR rates for HCV genotype 1b-infected patients.

Year of approval	TREATMENT	STUDY	Patients	Number of patients	Regimen and treatment duration	SVR	Reference
2011	TELAPREVIR / IFN-RBV	ADVANCE	Treatment-naïve patients with or without cirrhosis	151	48 wk PegIFN/RBV	48%	[64]
				151	8 wk TEL/ PegIFN/RBV + 4 wk PegIFN/RBV	74%	
				149	12 wk TEL/ PegIFN/RBV	79%	
		REALIZE	Treatment-experienced patients with or without cirrhosis	61	48 wk PegIFN/RBV	13%	[65]
				239	12 wk TEL + 48 wk PegIFN/RBV or 4 wk PegIFN/RBV, followed by 12 wk TEL + 48 wk PegIFN/RBV	72%	
	BOCEPREVIR/ IFN-RBV	SPRINT-2	Treatment-naïve patients without cirrhosis	121	48 wk PegIFN/RBV	40%	[66]
				124	4 wk PegIFN/RBV, followed by 24 wk BOC/ PegIFN/RBV	66%	
				117	4 wk PegIFN/RBV, followed by 44 wk BOC/ PegIFN/RBV	70%	
		RESPOND-2	Treatment-experienced patients with or without cirrhosis	34	48 wk PegIFN/RBV	22%	[67]
				66	4 wk PegIFN/RBV, followed by 32 wk BOC/ PegIFN/RBV	65%	

				61	4 wk PegIFN/RBV, followed by 44 wk BOC/ PegIFN/RBV	73%	
2013	**SIMEPREVIR - SOFOSBUVIR**	**OPTIMIST-1**	Treatment-naïve and treatment-experienced patients without cirrhosis	39	8 wk SOF + SIM	92%	[68]
				39	12 wk SOF + SIM	97%	
		OPTIMIST-2	Treatment-naïve or treatment experienced patients with cirrhosis	31	12 wk SOF + SIM	84%	[69]
2014	**LEDIPASVIR-SOFOSBUVIR**	**ION-1**	Treatment-naïve patients with or without cirrhosis	66	12 wk LDV + SOF	100%	[70]
				67	12 wk LDV + SOF + RBV	100%	
				68	24 wk LDV + SOF	97%	
				71	24 wk LDV + SOF + RBV	100%	
		ION-2	Treatment-experienced patients with or without cirrhosis	23	12 wk LDV + SOF	87%	[71]
				23	12 wk LDV + SOF + RBV	100%	
				24	24 wk LDV + SOF	100%	
				23	24 wk LDV + SOF + RBV	100%	
		ION-3	Treatment- naïve patients without cirrhosis	43	8 wk LDV + SOF	98%	[72]
				44	8 wk LDV + SOF + RBV	95%	

				44	12 wk LDV + SOF	98%	
	OMBITASVIR-PARITAPREVIR-RITONAVIR AND DASABUVIR	**SAPPHIRE-I**	Treatment- naïve patients without cirrhosis	151	12 wk PTV/r– OBV–DAV + RBV	98%	[73]
		SAPPHIRE-II	Treatment-experienced patients without cirrhosis	123	12 wk PTV/r– OBV –DAV + RBV	97%	[74]
		PEARL-III	Treatment-naïve patients without cirrhosis	210	12 wk PTV/r– OBV –DAV + RBV	99.5%	[75]
				209	12 wk PTV/r– OBV –DAV	99%	
		TURQUOISE-II	Treatment-naïve and treatment-experienced patients with compensated cirrhosis	68	12 wk PTV/r– OBV –DAV + RBV	98.5%	[76]
				51	24 wk PTV/r– OBV –DAV + RBV	100%	
2015	**DACLATASVIR-SOFOSBUVIR**	**ALLY-2**	Treatment-naïve and treatment-experienced patients with HIV-1 coinfection, with or without cirrhosis	6 (treatment-naïve)	8 wk DCV + SOF	50%	[77]
				12 (treatment-naïve)	12 wk DCV + SOF	100%	
				11 (treatment-experienced)		100%	
	ELBASVIR-GRAZOPREVIR	**C-EDGE**	Treatment-naïve patients with or without cirrhosis	131	12 wk EBV + GZP	99%	[78]
	SOFOSBUVIR-	**ASTRAL-1**	Treatment-naïve and treatment-experienced	94 (without cirrhosis)	12 wk SOF + VEL	100%	[79]

2016	**VELPATASVIR**		patients with or without cirrhosis	24 (with cirrhosis)		96%	
	DACLATASVIR-ASUNAPREVIR-BECLABUVIR (DVC-TRIO)	**UNITY-1**	Treatment-naïve and treatment-experienced patients without cirrhosis	83 (treatment-naïve)	12 wk DCV TRIO	97.6%	[53]
				28 (treatment-experienced)		100%	
		UNITY-2	Treatment-naïve and treatment-experienced patients with or without cirrhosis	17 (treatment-naïve)	12 wk DCV TRIO	100%	[54]
				15 (treatment-naïve)	12 wk DCV TRIO + RBV	100%	
				10 (treatment-experienced)	12 wk DCV TRIO	90%	
				10 (treatment-experienced)	12 wk DCV TRIO + RBV	100%	
		UNITY-3	Treatment-naïve and treatment-experienced patients with or without cirrhosis	149 (treatment-naïve)	12 wk DCV TRIO	96%	[55]
				64 (treatment-experienced)		97%	
		UNITY-4	Treatment-naïve and treatment-experienced patients with or without cirrhosis	128 (treatment-naïve)	12 wk DCV TRIO	100%	[56]
				29 (treatment-experienced)		100%	
2017	**GLECAPREVIR-PIBRENTASVIR**	**ENDURANCE-1**	Treatment-naïve and treatment-experienced patients without cirrhosis	198	8 wk GLE + PIB	100%	[80]
				203	12 wk GLE + PIB	100%	

Abbreviations: Boceprevir (BOC); Dasabuvir (DAV); Daclatasvir (DCV); Daclastasvir-Asunaprevir-Beclabuvir (DCV-TRIO); Elbasvir (EBV); Glecaprevir (GLE); Grazoprevir (GZP); Pegylated Interferon-Ribavirin (PegIFN/RBV); Ledipasvir (LDV); Ombitasvir (OBV);

Pibrentasvir (PIB); Paritaprevir–ritonavir (PTV–r); Ribavirin (RBV); Simeprevir (SIM); Sofosbuvir (SOF); Sustained virological response (SVR); Telaprevir (TEL); Velpatasvir (VEL); week (wk).