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VIRAL HEPATITIS

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Daclatasvir plus sofosbuvir, with or without ribavirin, for hepatitis C virus genotype 3 in a French early access programme

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Abstract

Background & Aims: Optimally effective treatment for hepatitis C virus genotype 3 (GT3) is urgently needed, particularly in advanced liver disease. Daclatasvir plus sofosbuvir was efficacious in phase 3 studies. Real-world data for daclatasvir+sofosbuvir in advanced GT3 infection are presented from the French Temporary Authorisation for Use programme, which allowed patients in need without other treatment options access to daclatasvir ahead of its market authorization.

Methods: Patients with F3/F4 fibrosis and/or extrahepatic hepatitis C virus manifestations, post-liver transplant hepatitis C virus recurrence and/or indication for liver/kidney transplant, were treated with daclatasvir+sofosbuvir (60+400 mg daily) for a recommended duration of 24 weeks. Addition of ribavirin and/or shorter treatment was at physician's discretion. The primary efficacy analysis was sustained virological response at post-treatment week 12 (SVR12; modified intention-to-treat). Safety was assessed by spontaneous adverse event reporting.

Results: The efficacy population comprised 333 patients, mostly cirrhotic (77%, of whom 18% were decompensated) and treatment experienced (72%). After 24 weeks of daclatasvir+sofosbuvir, SVR12 was 89% (174/196) overall (95% CI 83.6-92.5%), 98% (43/44) without cirrhosis (95% CI 88.2-99.6%) and 86% (129/150) with any degree of cirrhosis (95% CI 79.5-90.7%), without SVR12 increase in those who received additional ribavirin for 24 weeks (SVR12 82% [50/61; 95% CI 70.5-89.6%]). Among 516 GT3-infected patients with safety data, 5 discontinued for adverse events and 11 died.

Conclusions: Daclatasvir+sofosbuvir achieved high SVR12 rates and was well tolerated in this large real-world cohort of GT3-infected patients with advanced liver disease, without benefit of ribavirin in those treated 24 weeks.

KEYWORDS

compassionate use, daclatasvir, genotype 3, hepatitis C, real-world data, sofosbuvir

1 | INTRODUCTION

Hepatitis C virus (HCV) genotype 3 is the second most prevalent genotype worldwide,[1] and associated with several features, such as accelerated progression of fibrosis and a greater risk of steatosis and hepatocellular carcinoma (HCC),[2–4] that significantly increase liver-related hospitalization and death relative to other genotypes.[5] Thus, there is an urgent need for safe and effective treatment of genotype 3 infection.

All-oral HCV regimens have greatly improved treatment safety and efficacy relative to treatment with pegylated interferon (pegIFN) and ribavirin (RBV). However, some current oral agents have limited activity against genotype 3. Daclatasvir (DCV), a non-structural protein 5A (NS5A) inhibitor, and sofosbuvir (SOF), a non-structural protein 5B (NS5B) inhibitor, are pan-genotypic oral HCV antivirals with potent activity against genotype 3.[6,7] In the phase 3 ALLY-3 study, 12 weeks of DCV+SOF treatment resulted in a 96% rate of sustained virological response at post-treatment week 12 (SVR12) in non-cirrhotic patients with genotype 3.[8] This regimen is now a recommended option for non-cirrhotic genotype 3 infection in several clinical guidelines, including the European Association for the Study of the Liver, the American Association for the Study of Liver Diseases and the Association Française pour l'Etude du Foie guidelines.[9–11]

- A real-world early access programme treated HCV genotype 3-infected patients with highly advanced disease and no other treatment options with daclatasvir plus sofosbuvir. Many would have been ineligible for a randomized study.
- Sustained virological response after 24 weeks of treatment was 89%: 98% without cirrhosis; 86% with cirrhosis (including decompensated cirrhosis). There was no incremental benefit with concomitant ribavirin.
- Only 1% of patients were recorded to have discontinued for an adverse event.
- Daclatasvir and sofosbuvir, with or without ribavirin, was effective and well tolerated in this real-world cohort of HCV genotype 3-infected patients with advanced disease.

Genotype 3 is more difficult to treat in patients with cirrhosis. An SVR12 rate of 86% was observed among genotype 3-infected patients with compensated cirrhosis following 12 or 16 weeks of

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATU, Autorisation Temporaire d'Utilisation; CYP3A4, cytochrome P450 3A4; DCV, daclatasvir; gamma GT, gamma-glutamyl transferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ITT, intention-to-treat; LLOQ, lower limit of quantification; MELD, Model for End-Stage Liver Disease; mITT, modified intention-to-treat; NS5A, non-structural protein 5A; NS5B, non-structural protein 5B; pegIFN, pegylated interferon; PT12, post-treatment week 12; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virological response at PT12; TAR, Treatment Access Request; VA, Veterans Administration.

DCV+SOF+RBV in the phase 3 ALLY-3+ study.[12] The combination of DCV+SOF for 24 weeks, with or without RBV, is a recommended option for genotype 3 infection with cirrhosis in several guidelines,[9–11] but there are few empirical data for this duration.

Early access initiatives allow access to promising new drugs ahead of their marketing authorization for patients with high unmet needs. Real-world data from such initiatives are valuable for validating clinical study data in a broader patient population. Globally, more than 7000 patients have been referred for treatment under early access programmes for DCV (Data on File [Bristol-Myers Squibb 2016: DACL-047]). The French Autorisation Temporaire d'Utilisation (ATU) programme is one of the largest: ≈4000 HCV-infected patients with severe liver disease and/or recurrent infection were enrolled for treatment with DCV+SOF with or without RBV, most receiving 24 weeks of treatment. We present analyses of a subgroup of ATU patients with genotype 3 infection.

2 | PATIENTS AND METHODS

2.1 | Patients

Patients enrolled in the ATU programme infected with HCV genotype 3 were included. Eligible patients were adults with chronic HCV infection, no alternative treatment options and an indication for treatment as a result of (i) advanced liver disease (physician-assessed F3 or F4 METAVIR or METAVIR-equivalent fibrosis and/or severe extrahepatic HCV manifestations), (ii) post-liver transplant HCV recurrence or (iii) an indication for a liver or kidney transplant.

2.2 | Determination of cirrhosis

Enrolled patients were assigned a cirrhosis status on the basis of a hierarchical algorithm (Table S1) based on information provided in the Treatment Access Request (TAR). The algorithm considered (i) the patient's reported fibrosis stage (F0-F4) by any method of assessment, (ii) any FibroScan result provided and (iii) the stage of disease described in the patient's eligibility for ATU treatment. Patients with reported F4 fibrosis were considered cirrhotic. Those <F4 or missing data were considered cirrhotic with an accompanying FibroScan result ≥14.5 kPa. If FibroScan data were missing or inconsistent with the reported fibrosis, the stage of disease was used.

Patients with cirrhosis were further categorized by Child-Pugh class as compensated (Child-Pugh A) or decompensated (Child-Pugh B or C).

2.3 | Treatment dose and duration

Recommended treatment was DCV 60 mg+SOF 400 mg, once daily, for 24 weeks. RBV could be added and/or shorter treatment undertaken at the physician's discretion. DCV 30 mg was recommended with ritonavir-boosted atazanavir or other potent inhibitors of cytochrome P450 3A4 (CYP3A4) or P-glycoprotein; and DCV 90 mg with efavirenz or other moderate inducers of CYP3A4. DCV was contraindicated with potent CYP3A4 or P-glycoprotein inducers, and not recommended in pregnancy or women of childbearing potential not using effective contraception.

2.4 | Programme conduct

This was not a clinical trial, and treatment was undertaken according to standard clinical practice. In accordance with French regulations, the ATU cohort was approved by the French authorities; neither ethics committee approval nor written informed consent was required, and data protection was ensured. TAR forms for individual patients were submitted to the programme sponsor (BMS) by their treating physicians and, once a TAR was granted, the patient's institutional pharmacy could order DCV directly from the sponsor. SOF was not provided through the sponsor.

Physicians were invited to return completed visit forms to the sponsor at treatment initiation (day 0), treatment weeks 2, 4, 8, 12, 16, 20 and 24 (as appropriate), post-treatment weeks 4, 12 (PT12) and 24 and treatment discontinuation. Forms reporting pregnancy or adverse events (AEs) were provided by physicians as appropriate. Physicians reporting AEs were not asked to clarify the data.

2.5 | Assessments

Hepatitis C virus-RNA was assessed by local laboratories using their own protocols. For each returned visit form, quantitative HCV-RNA data were provided along with the assay and lower limit of quantification (LLOQ) used, and an outcome of "quantifiable" (>LLOQ) or "unquantifiable" (≤LLOQ) was assigned. Where a qualitative result was reported, HCV-RNA was considered unquantifiable if target RNA was undetected.

Safety was evaluated as frequencies of serious AEs, AEs and discontinuations for AEs. The physician was responsible for AE reporting. Standard pharmacovigilance practice was used, imputing AEs of unreported causality as treatment related.

2.6 | Analysis of populations and endpoints

The treated (safety) population comprised all patients with ≥1 post-day 0 visit form or AE report; the intention-to-treat (ITT) population was the subset with detectable baseline HCV-RNA and >1 day of treatment.

The primary efficacy analysis was a modified ITT (mITT) approach which excluded ITT patients without virological data at PT12 because of discontinuation or dropout for reasons other than predefined treatment failure.

The primary efficacy outcome was SVR12, defined as unquantifiable HCV-RNA at PT12. Treatment failure was failure to achieve SVR12 for defined virological or non-virological reasons. Virological failure consisted of virological breakthrough (quantifiable on-treatment HCV-RNA from week 2 following an unquantifiable measure), relapse (unquantifiable HCV-RNA at end-of-treatment, then quantifiable at PT12) or undefined failure (quantifiable HCV-RNA at all reported visits). Non-virological failure comprised missing HCV-RNA at PT12 as a result of treatment discontinuation for AEs or death on/after treatment. An observed value analysis was also performed which excluded non-virological failures.

2.7 | Statistical analysis

Missing PT12 data were back-imputed from the next available measurement; other intermittent missing data were imputed as the worse of the two flanking outcomes.

DCV treatment duration was derived from the documented start and end dates. Start date was taken from the listed date for DCV initiation, the pharmacovigilance database or the date of day 0. Treatment end was as listed in the treatment discontinuation form or the last DCV discontinuation date with no new dose or resumption, taken from the pharmacovigilance database or imputed from the last on-treatment visit. Primary analyses were based on actual treatment duration, analysed as 12 weeks (≤14 weeks of actual treatment) or 24 weeks (>14 weeks). Sensitivity analyses were undertaken for the duration initially considered by the physician (reported in the TAR), and for actual durations <10, 10-<14, 14-<20 and ≥20 weeks.

3 | RESULTS

3.1 | Patients

A total of 560 genotype 3-infected patients referred by 280 physicians were enrolled from 4 March to 27 October 2014. From these, a treated population of 516 and an mITT efficacy population of 333 patients were derived (Figure 1A).

Baseline characteristics (mITT population) are shown in Table 1. Patients were primarily treatment experienced (72%), of whom 60% had prior relapse, 21% null response and 19% partial response. Cirrhosis was present in 77% (18% of whom were decompensated), and 19% of 145 cirrhotic or pretransplant patients with data had a Model for End-Stage Liver Disease (MELD) score ≥15. Baseline albumin was <35 g/L in 27%; baseline HCV-RNA ≥6 million IU/mL in 50%, and 14% were co-infected with human immunodeficiency virus (HIV). Baseline characteristics for the 138 ITT patients excluded from the mITT analysis were similar to the 333 mITT patients (Table S2); only Child-Pugh stage at TAR showed a $P<.05$ difference, with more Child-Pugh C (10% vs 3%) and slightly fewer Child-Pugh B (11% vs 15%) patients among those excluded. Trends ($P<.1$) towards more HIV or hepatitis B virus (HBV) co-infection and lower aspartate aminotransferase (AST) and gamma-glutamyl transferase (gamma GT) among excluded patients were also observed.

Most patients (59% [196/333]) received DCV+SOF without RBV for 24 weeks (as analysed), and a further 20% (66/333) for 12 weeks. The remaining 21% (71/333) received DCV+SOF+RBV, mostly (86% [61/71]) for 24 weeks. Forty-seven per cent (34/72) in the 12-week analysis groups, and 88% (221/251) in the 24-week groups, were initially considered for 12 or 24 weeks of treatment respectively (Figure 1B). For those treated 24 weeks, patients receiving RBV had more baseline cirrhosis (90% vs 77% without RBV) and encephalopathy (7% vs<1%), less HIV co-infection (5% vs 18%), a shorter time since HCV diagnosis (median 11.5 vs 15.4 years), higher total bilirubin (median 19.5 vs 14.0 μmol/L) and lower alanine aminotransferase (ALT) at TAR (median 76.0 vs 107.0 IU/L), and lower HCV-RNA (median 5.8 vs 6.2 $\log_{10}$ IU/mL) and platelets (median 94.0 vs 128.5×10^9/L) at day 0 (all comparisons $P<.05$).

3.2 | Virological response

Overall SVR12 rates and causes of treatment failure are shown in Table 2 for the primary (actual duration) and sensitivity analyses (duration initially considered). For patients who received DCV+SOF for 24 weeks, overall SVR12 (mITT) was 89% (86% with cirrhosis, 98% without) and was similar with and without prior HCV treatment (90% [130/145; 95% CI 84-94%] vs 88% [42/48; 95% CI 75-94%] respectively). Among treatment-experienced cirrhotic patients in the primary analysis, SVR12 was 87% without RBV (101/116; 95% CI 80-92%) and 80% with RBV (32/40; 95% CI 65-90%). No incremental SVR12 advantage was seen in patients who received RBV.

Sustained virological response at PT12 was numerically lower in patients with a 12-week analysed duration, driven by more treatment failure for AEs or death (8% [6/76] vs 2% [4/257]) or undefined virological failures (8% [6/76] vs 1% [3/257]) than the 24-week group, and a high proportion of patients treated less than 12 weeks. Almost one-fifth of 12-week patients (18% [14/76]) received <10 weeks of actual treatment (13% [10/76] for <6 weeks), and these had very low rates of SVR12 (Figure 2); among the 10 patients treated <10 weeks with treatment failure, only 2 (7 and 9 weeks) received >4 weeks of treatment, and both had non-virological failure. In contrast, those who received 10-14 weeks of actual therapy had 80% SVR12 overall; 96% without cirrhosis and a 70% rate with cirrhosis (Figure 2), likely because of low RBV use among patients treated for this duration (6/62 [10%]).

Overall, patients treated without RBV had similar SVR12 rates by either analysed or initially considered treatment duration. Among patients treated with RBV, SVR12 was higher in those initially considered for 12 weeks of treatment than those analysed as receiving 12 weeks (89% vs 60%) because of four patients who actually received 24 weeks (three achieved SVR12). Patients initially considered for 24 weeks of DCV+SOF+RBV had a slightly lower SVR12 than those who received 24 weeks (75% vs 82%), driven by four patients analysed as receiving 12 weeks because of early treatment failure (one discontinuation for an AE; two with a last recorded HCV-RNA quantifiable at week 2 or 4; one virological breakthrough).

Table 3 shows SVR12 rates (primary analysis) for patients with or without cirrhosis. Among patients with cirrhosis, SVR12 was numerically higher in the 24-week groups (86% [129/150] without RBV and 82% [45/55] with RBV) and also higher in compensated (Child-Pugh A) cirrhosis (9% [9/103 with MELD data] of whom had a MELD score ≥15) than in decompensated (Child-Pugh B or C) disease (59% [18/31 with MELD data] of whom had a MELD score ≥15; Table S3). Of patients treated 24 weeks with or without RBV, 88% (129/147) with compensated cirrhosis achieved SVR12 compared with 74% (23/31) with decompensated disease. Although decompensated patient numbers were small, there was no apparent effect on SVR12 of RBV for 24 weeks in either compensated or decompensated patients.

3.3 | Treatment failure

There were 55 treatment failures: 45 virological (4 breakthroughs, 32 relapses, 9 undefined) and 10 non-virological failures for death

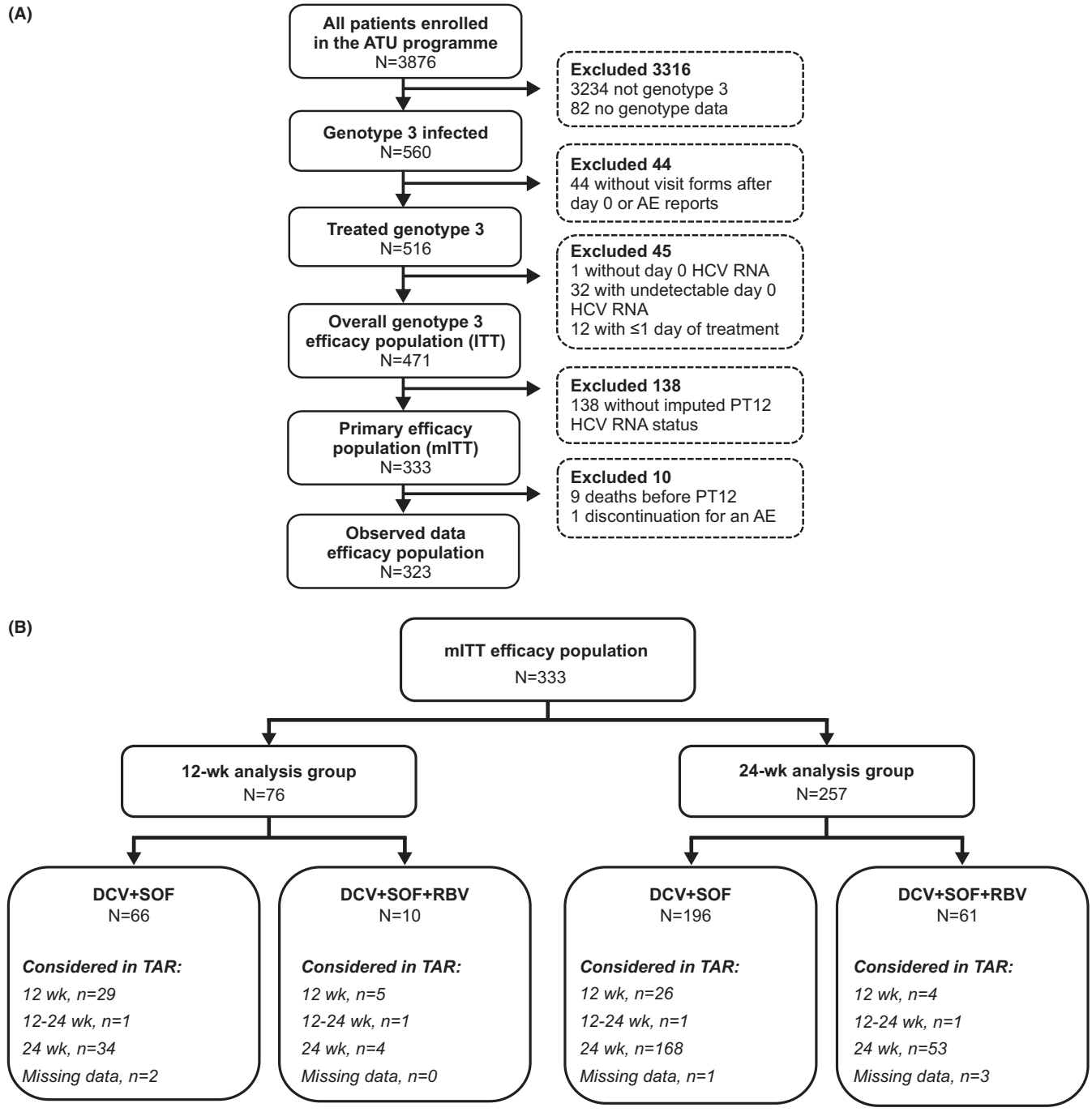

FIGURE 1 Derivation of the analysis populations. AE, adverse event; ATU, Autorisation Temporaire d'Utilisation; DCV, daclatasvir; HCV, hepatitis C virus; ITT, intention-to-treat; mITT, modified intention-to-treat; PT12, post-treatment week 12; RBV, ribavirin; SOF, sofosbuvir; TAR, Treatment Access Request; wk, weeks

(n=9) or treatment discontinuation for an AE (n=1; ascites/hepatocellular carcinoma/encephalopathy/pneumonia). All undefined virological failures were in patients whose last available HCV-RNA data through PT12 was a quantifiable reading at treatment week 2 or 4.

Individual characteristics of these 55 patients are shown in Table S4, and aggregate characteristics for virological and non-virological failures vs SVR12 successes in Table S5. Overall, patients with treatment failure showed more advanced indicators of baseline liver disease—more decompensated cirrhosis and MELD scores ≥15, lower platelets and albumin, and higher gamma GT—than patients who achieved SVR12. This trend was particularly marked in patients with non-virological failure, of whom 70% had decompensated cirrhosis and 57% MELD ≥15, along with more laboratory abnormalities than those with virological failure or achieving SVR12.

3.4 | Liver disease measures pre- and post-treatment

Paired baseline and PT12 Child-Pugh data were available in 67 patients and MELD score in 46 patients.

TABLE 1 Baseline characteristics

Parameter, n (%) unless otherwise indicated	DCV+SOF 12 wk (n=66)	DCV+SOF+RBV 12 wk (n=10)	DCV+SOF 24 wk (n=196)	DCV+SOF+RBV 24 wk (n=61)	Overall (N=333)
Age, median (range), years	54.1 (39-78)	52.2 (44-64)	55.0 (27-79)	53.5 (40-72)	54.2 (27-79)
Male	48 (74)	6 (60)	145 (75)	46 (79)	245 (75)
HCV-RNA at day 0, median (IQR) log_{10}IU/mL	5.9 (5.2-6.4)	5.7 (5.5-6.1)	6.2 (5.6-6.5)	5.8 (5.3-6.1)	6.0 (5.4-6.4)
HCV-RNA ≥6 log_{10} IU/mL	29 (44)	4 (40)	112 (58)	20 (33)	165 (50)
Advanced fibrosis (F3)	16 (24)	2 (20)	28 (15)	2 (3)	48 (15)
Cirrhosis	43 (65)	8 (80)	150 (77)	55 (90)	256 (77)
Child-Pugh class[a]					
A	32 (76)	8 (100)	111 (85)	36 (75)	187 (82)
B	7 (17)	0	17 (13)	11 (23)	35 (15)
C	3 (7)	0	2 (2)	1 (2)	6 (3)
MELD category at day 0					
<10	20 (57)	6 (86)	39 (57)	16 (46)	81 (56)
10 to <15	8 (23)	0	16 (24)	13 (37)	37 (26)
≥15	7 (20)	1 (14)	13 (19)	6 (17)	27 (19)
Hepatocellular carcinoma	1 (2)	1 (10)	19 (10)	6 (10)	27 (8)
Extrahepatic manifestations	10 (15)	0	20 (11)	3 (5)	33 (10)
Without F3 or F4 fibrosis	7 (11)	0	10 (5)	1 (2)	18 (6)
Post-liver transplant HCV recurrence	3 (5)	0	21 (11)	6 (10)	30 (9)
Preliver/renal transplant	5 (8)	0	17 (9)	8 (13)	30 (9)
Treatment experienced	41 (62)	7 (70)	145 (75)	44 (72)	237 (72)
SOF experienced	1 (2)	1 (10)	9 (5)	4 (7)	15 (5)
Co-infection with HIV/HBV	5 (8)/0	4 (40)/0	35 (18)/5 (3)	3 (5)/2 (3)	47 (14)/7 (2)
Laboratory test results at TAR, median (IQR)					
Platelets, $\times10^9$/L	126 (84-178)	128 (69-162)	127 (85-181)	97 (67-147)	122 (80-173)
Albumin, g/L	38 (33-42)	39 (35-40)	38 (35-42)	38 (33-42)	38 (34-42)
ALT, IU/L	84 (53-138)	107 (77-110)	107 (54-155)	76 (50-111)	93 (53-143)
AST, IU/L	81 (57-119)	98 (47-147)	93 (58-144)	91 (56-124)	88 (57-136)
Total bilirubin, µmol/L	14 (9-24)	10 (7-18)	14 (9-21)	20 (12-33)	15 (9-24)
Gamma GT, IU/L	114 (55-176)	92 (49-145)	94 (64-156)	95 (65-180)	95 (62-168)
Laboratory abnormalities at day 0[b]					
Platelets <50×10^9/L	6 (10)	2 (20)	13 (7)	6 (11)	27 (8)
Albumin <35 g/L	17 (29)	2 (22)	39 (25)	17 (35)	75 (27)
ALT >175 IU/L	11 (17)	1 (10)	32 (17)	6 (11)	50 (15)
AST >200 IU/L	6 (9)	3 (30)	16 (8)	2 (4)	27 (8)
Total bilirubin >60 µmol/L	3 (5)	0	5 (3)	2 (5)	10 (4)
Gamma GT >90 (women) or >140 (men) IU/L	23 (39)	3 (38)	61 (34)	20 (39)	107 (36)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCV, daclatasvir; gamma GT, gamma-glutamyl transferase; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile (25th-75th) range; MELD, Model for End-Stage Liver Disease; RBV, ribavirin; SOF, sofosbuvir; TAR, Treatment Access Request; wk, weeks.

Characteristics are at TAR except where indicated as day 0. Percentages are of patients with available data in indicated category. Missing data for percentages quoted: sex (n=6); previous HCV treatment (n=3); cirrhosis (n=2); Child-Pugh class (n=28); MELD score (n=116); extrahepatic manifestations (n=6); fibrosis stage (n=5); platelets (n=15); albumin (n=57); ALT (n=9); AST (n=11); total bilirubin (n=70); gamma GT (n=37).

[a]Cirrhotic patients only.

[b]Grade ≥3 except for albumin.

TABLE 2 Sustained virological response and treatment failure

	DCV+SOF 12 wk	DCV+SOF+RBV 12 wk	DCV+SOF 24 wk	DCV+SOF+RBV 24 wk	Total
Primary analysis (actual treatment duration)					
N					
mITT	66[a]	10[b]	196	61	333
Observed values[c]	61	9	193	60	323
SVR12, n (%) [95% CI]					
mITT	48 (73)	6 (60)	174 (89)	50 (82)	278 (83)
	[61.0-82.0]	[31.3-83.2]	[83.6-92.5]	[70.5-89.6]	[79.1-87.1]
Observed values[c]	48 (79)	6 (67)	174 (90)	50 (83)	278 (86)
	[66.9-87.1]	[35.4-87.9]	[85.1-93.6]	[72.0-90.7]	[81.9-89.4]
Treatment failure, n	18	4	22	11	55
Virological breakthrough	0	1	2	1	4
Relapse	9	0	14	9	32
Undefined virological failure[d]	4	2	3	0	9
Non-virological failure	5	1	3	1	10
Sensitivity analysis (treatment duration initially considered in TAR)					
N					
mITT	55	9	202	57	333[e]
Observed values[c]	53	9	197	55	323[f]
SVR12, n (%) [95% CI]					
mITT	40 (73)	8 (89)	178 (88)	43 (75)	278 (83)
	[59.8-82.7]	[56.5-98.0]	[82.9-91.9]	[62.9-84.8]	[79.1-87.1]
Observed values[c]	40 (75)	8 (89)	178 (90)	43 (78)	278 (86)
	[62.4-85.1]	[56.5-98.0]	[85.4-93.7]	[65.6-87.1]	[81.9-89.4]
Treatment failure, n	15	1	24	14	55
Virological breakthrough	1	0	1	2	4
Relapse	9	1	14	8	32
Undefined virological failure[d]	3	0	4	2	9
Non-virological failure	2	0	5	2	10

DCV, daclatasvir; mITT, modified intention-to-treat; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virological response at post-treatment week 12; TAR, Treatment Access Request; wk, weeks.

Non-virological failure: treatment discontinuation for adverse events or death before post-treatment week 12.

[a]10 patients with cirrhosis received <10 wk of treatment (8 for <6 wk) of whom seven were treatment failures.

[b]Four patients with cirrhosis received <10 wk of treatment (two for <6 wk) and three were treatment failures.

[c]Excludes non-virological treatment failure.

[d]Last reported HCV-RNA through post-treatment week 12 was at treatment week 2 or 4 (quantifiable) in all cases.

[e]Total includes 10 patients with a considered duration of 12-24 wk (n=4) or missing data (n=6).

[f]Total includes nine patients with a considered duration of 12-24 wk (n=3) or missing data (n=6).

At PT12, Child-Pugh class improved in 69% (9/13) of patients with decompensated cirrhosis (class B to A, n=7; class C to A, n=2), remained unchanged in 15% (2/13; both class B), and worsened in 15% (2/13; both class B to C). Among 54 patients with Child-Pugh A cirrhosis, 96% (52/54) remained unchanged at PT12 and 4% (2/54) progressed to class B.

All patients (n=24) with MELD scores <10 and paired data remained <10 at PT12. Of 12 patients with MELD scores 10-<15, 58% (7/12) were <10 at PT12, and the rest unchanged. Of 10 patients with MELD scores ≥15, 50% (5/10) improved at PT12 (two dropped to <10, three to 10-<15), while the remaining 5 remained unchanged.

3.5 | Safety

On-treatment safety (treated population) is shown in Table 4. Overall there were 11 deaths (including nine non-virological treatment failures in the mITT population): seven with decompensated cirrhosis, two compensated cirrhosis and two without cirrhosis. Eight deaths were reported as unrelated to treatment and three (two unknown/unreported cause in Child-Pugh B cirrhosis; multi-organ failure/septic shock/intestinal obstruction after PT12 in a patient with SVR12 considered non-cirrhotic for missing data) were of unreported

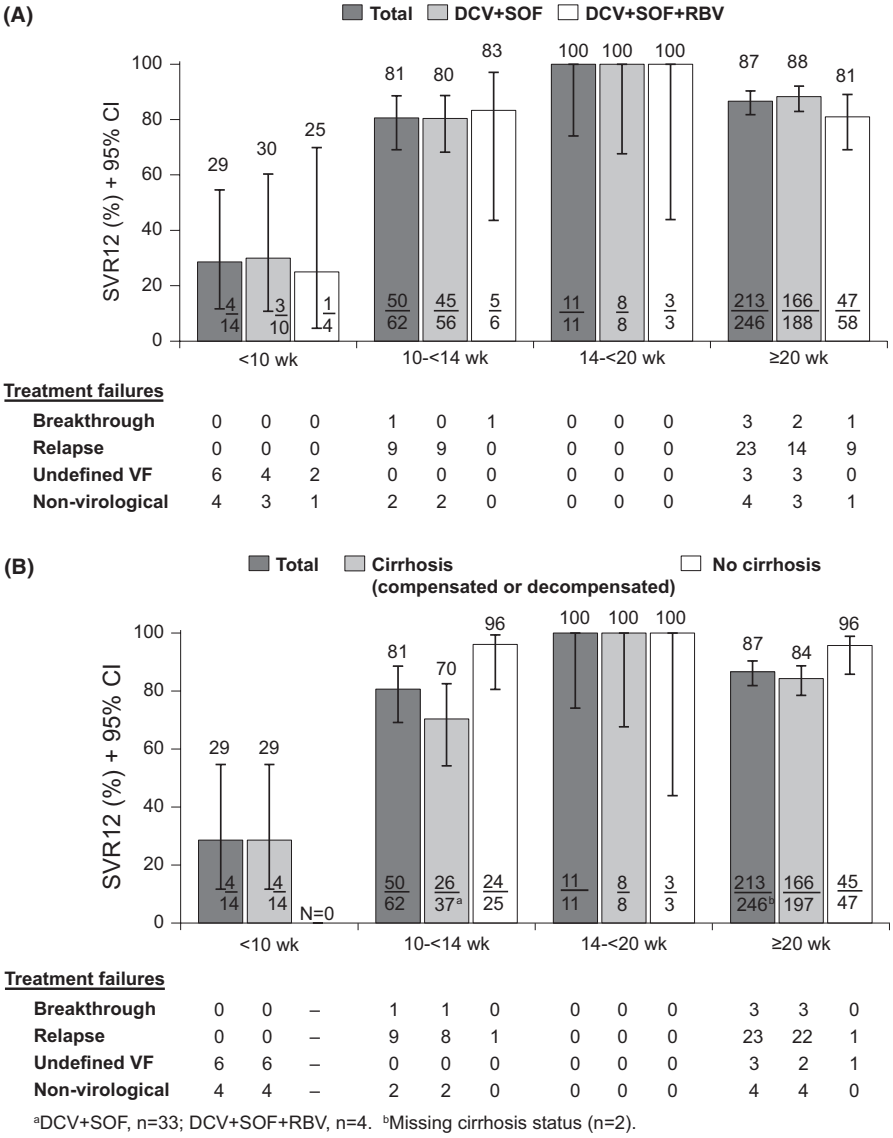

FIGURE 2 Sustained virological response (mITT) according to actual duration of treatment received by (A) treatment regimen; (B) cirrhosis status. DCV, daclatasvir; RBV, ribavirin; SOF, sofosbuvir; VF, virological failure; wk, weeks

causality, and hence were categorized as treatment related under pharmacovigilance imputation. Five patients discontinued for AEs, three achieved SVR12 (neutropenia, allergic dermatitis, unreported event); one was a non-virological treatment failure (see above) and one requested treatment interruption in combination with an unspecified AE (excluded from the ITT population for unquantifiable baseline HCV-RNA).

More serious AEs occurred among patients receiving RBV, but with no apparent influence of treatment duration (Table 4). Compared with patients with available data not receiving RBV (n=395), those receiving RBV (n=109) experienced more serious gastrointestinal (10% vs 4%), hepatobiliary (5% vs 2%) and psychiatric disorders (4% vs 1%) and more neoplasms (7% vs 3%), consistent with the trend towards more advanced baseline disease observed in patients prescribed RBV. Three patients experienced a grade 3/4 reduction in haemoglobin (lowest on-treatment level 7.5-7.8 g/dL); none were receiving RBV.

Overall, the incidence of AEs in cirrhotic patients with baseline MELD data was similar between those with low (<10; n=134), intermediate (10-<15; n=56) and high (≥15; n=40) MELD scores (37%, 32%, 40% respectively). However, serious AEs were more common for scores ≥15 than <15 (30% vs 14%), particularly gastrointestinal disorders (15% vs 5%); infections/infestations, nervous system disorders and hepatobiliary disorders (each 13% vs 2%); and metabolism/nutrition disorders (8% vs 2%). Death was also more common for MELD ≥15 than <15 (10% vs 1%).

4 | DISCUSSION

Hepatitis C virus genotype 3 has generally proven more challenging to treat with oral antivirals than other genotypes. This large real-world cohort of patients with genotype 3 infection plus advanced liver disease provides data on the clinical effectiveness of DCV+SOF (±RBV) in a challenging subset of patients with very limited options. Among these, overall SVR12 rates of 89% without RBV and 82% with RBV were observed after 24 weeks of treatment.

TABLE 3 Sustained virological response and treatment failure by cirrhosis status (primary analysis: actual treatment duration)

	DCV+SOF 12 wk	DCV+SOF+RBV 12 wk	DCV+SOF 24 wk	DCV+SOF+RBV 24 wk	Total
Patients without cirrhosis					
N					
mITT[a]	23	2	44	6	75
SVR12, n (%) [95% CI]					
mITT	22 (96) [79.0-99.2]	2 (100) [34.2-100]	43 (98) [88.2-99.6]	5 (83) [43.6-97.0]	72 (96) [88.9-98.6]
Treatment failure, n	1	0	1	1	3
Virological breakthrough	0	-	0	0	0
Relapse	1	-	0	1	2
Undefined virological failure[b]	0	-	1	0	1
Non-virological failure	0	-	0	0	0
Patients with cirrhosis					
N					
mITT	43	8	150	55	256
Observed values[c]	38	7	147	54	246
SVR12, n (%) [95% CI]					
mITT	26 (60) [45.6-73.6]	4 (50) [21.5-78.5]	129 (86) [79.5-90.7]	45 (82) [69.7-89.8]	204 (80) [74.3-84.2]
Observed values[c]	26 (68) [52.5-80.9]	4 (57) [25.0-84.2]	129 (88) [81.5-92.1]	45 (83) [71.3-91.0]	204 (83) [77.7-87.1]
Treatment failure, n	17	4	21	10	52
Virological breakthrough	0	1	2	1	4
Relapse	8	0	14	8	30
Undefined virological failure[b]	4	2	2	0	8
Non-virological failure	5	1	3	1	10

DCV, daclatasvir; mITT, modified intention-to-treat; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virological response at post-treatment week 12; wk, weeks.
Excludes two patients of unreported cirrhosis status (both DCV+SOF for 24 wk).
Non-virological failure: treatment discontinuation for adverse events or death before post-treatment week 12.
[a]No patient had non-virological failure; observed values analysis not shown.
[b]Last reported HCV-RNA through post-treatment week 12 was at treatment week 2 or 4 (quantifiable) in all cases.
[c]Excludes non-virological treatment failure.

The majority (62% [48/77]) of non-cirrhotic patients had advanced (F3) fibrosis, and their 96% SVR12 rate (mITT) after 12 or 24 weeks of DCV+SOF±RBV is similar to non-cirrhotic patients treated with DCV+SOF for 12 weeks in ALLY-3 (ITT 96%) and patients with F3 fibrosis treated for 12 or 16 weeks with DCV+SOF+RBV in ALLY-3+ (ITT 100%).[8,12] Although real-world and clinical study findings must be compared with caution, these data suggest that DCV+SOF without RBV for 12 weeks is effective in non-cirrhotic genotype 3 infection, including patients with advanced fibrosis.

For patients with cirrhosis, it was not possible to evaluate the impact of RBV in the 12-week analysis group owing to the small number receiving RBV (16% [8/51]) and the significant number with very short (<10 weeks) actual treatment durations (27% [14/51], including four receiving RBV). Thirty-seven patients with cirrhosis (compensated and decompensated) were treated for 10-14 weeks, most (89% [33/37]) without RBV, and their 70% SVR12 (mITT) rate was consistent with the 63% ITT rate in patients with compensated cirrhosis after 12 weeks of DCV+SOF in ALLY-3.[8] This suggests that RBV may be required for shorter (<24 week) treatment of genotype 3 infection with cirrhosis.

In contrast, SVR12 by mITT for cirrhotic patients treated for 24 weeks either with (82% [45/55]) or without RBV (86% [129/150]) was similar to that by ITT after 12 or 16 weeks of DCV+SOF+RBV in patients with compensated cirrhosis in ALLY-3+ (86%).[12] No additional benefit of RBV was observed in compensated or decompensated cirrhosis, although unrandomized treatment allocation and potential selection bias for RBV use makes it difficult to assess the significance of this. These data are consistent with other real-world findings from the European Union compassionate use programme, in which cirrhotic patients (52% decompensated) treated with DCV+SOF+RBV for 24 weeks received no SVR12 benefit over those treated without RBV (88% vs 89%).[13] Other real-world data in less clinically

TABLE 4 On-treatment safety summary by derived regimen (all treated patients; N=516)

n (%)	DCV+SOF 12 wk (n=98)	DCV+SOF+RBV 12 wk (n=24)	DCV+SOF 24 wk (n=297)	DCV+SOF+RBV 24 wk (n=85)	Missing Regimen (n=12)	Total (N=516)
Patients with ≥1 AE	38 (39)	8 (33)	103 (35)	41 (48)	3 (25)	193 (37)
Patients with ≥1 serious AE	12 (12)	5 (21)	34 (11)	21 (25)	2 (17)	74 (14)
Discontinuation because of AEs (excluding death)[a]	2 (2)	2 (11)	1 (<1)	0	NR	5 (1)
Deaths[b]	5 (5)	0	4 (1)	1 (1)	1 (8)	11 (2)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCV, daclatasvir; gamma GT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; NR, not reported; RBV, ribavirin; SOF, sofosbuvir.

[a]Neutropenia, dermatitis allergic, unreported event, ascites/HCC/encephalopathy/pneumonia, patient request/unreported AE (n=1 each).

[b]Deep vein thrombosis/pulmonary embolism (n=1); multi-organ failure/hepatorenal syndrome (n=1); septic shock with multi-organ failure/intestinal obstruction (n=1), peritonitis (n=1) or lymphoma/chronic hepatitis C/respiratory distress (n=1); haemorrhagic stroke (n=1); renal impairment (n=1); unknown/unreported cause (n=4).

advanced patients with genotype 3 infection from the US Veterans Administration (VA) healthcare system[14] and HCV-TARGET observational study[15] have demonstrated SVR rates of 81% and 82%, respectively, with a 12-week regimen of SOF+RBV+pegIFN. In addition, cirrhotic patients with genotype 3 treated for 12 weeks with SOF plus ledipasvir in the VA cohort had a lower SVR rate (65%),[14] as did similar patients treated for 24 weeks with SOF+RBV without pegIFN in the VA cohort (62%)[14] and in HCV-TARGET (45%),[15] emphasizing the challenging nature of this patient group in real-world settings.

Absolute SVR12 rates differed between compensated and decompensated patients. For Child-Pugh A cirrhosis, SVR12 (mITT) after 24 weeks of treatment was 89% (99/111) without RBV and 83% (30/36) with RBV, while for Child-Pugh B or C, SVR12 was 74% (14/19) without RBV and 75% (9/12) with RBV. The optimal regimen and treatment duration for decompensated cirrhosis remain to be determined. In the UK cohort of the European Union programme, decompensated genotype 3-infected patients had an SVR12 rate of 71% after 12 weeks of treatment with DCV+SOF+RBV.[16] However, as with the ATU programme, the European programme data are unrandomized, and the results cannot be easily extrapolated, particularly since very few decompensated genotype 3 patients received DCV+SOF without RBV in the UK cohort (n=5).

Although baseline measures of advanced liver disease, such as decompensated cirrhosis and high MELD scores, were associated with higher rates of treatment failure, death and serious AEs in the ATU programme, overall rates of death (2%) and discontinuations because of AEs (1%) were infrequent. Child-Pugh class and MELD score improved in the majority of decompensated or high-MELD patients for whom baseline and PT12 data were available, although the caveat applies that the number of paired measures was limited and largely restricted to patients achieving SVR12.

The ATU programme represents one of the largest observational assessments thus far of patients with HCV genotype 3 and advanced disease. However, as with all real-world data, there are limitations for interpretation. One important limitation is that drug allocation was not randomized; both treatment duration and use of RBV were entirely at the physician's discretion. This introduces a potential source of bias and an imbalance in group sizes that renders it impossible to fully assess the effect of RBV, particularly since it was more likely to have been prescribed to patients considered harder to treat. Another is that data collection and assessment were non-standardized and based on local practice, resulting in substantial intersite variability in the definitions of certain parameters and the frequency of follow-up, as well as a significant amount of missing data. A third limitation is that data were returned voluntarily; it was not possible to establish whether missing data were caused by loss to follow-up, and physicians may have provided follow-up information based on individual results, thus biasing an intention-to-treat analysis to underevaluate efficacy. Finally, collection of safety data was based on pharmacovigilance rather than continuous prospective assessment; it is therefore likely that AEs were under-reported.

Despite these limitations, observations from this cohort of patients with advanced disease—many of whom would not have been eligible for a clinical trial—are consistent with phase 3 studies of DCV+SOF±RBV, and with multinational real-world data from the European Union. All-oral treatment with DCV+SOF±RBV achieved high SVR12 rates and was well tolerated in HCV genotype 3-infected patients with advanced liver disease.

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CONFLICTS OF INTEREST

CH, VDL, FZ: personal fees from Abbvie, BMS, Gilead, Janssen, MSD. CH: personal fees from Roche. VDL: grants from Gilead. PL:

congress attendance for Biotest, Gilead; Sub-Principal Investigator for AbbVie. VDM: personal fees (advisory boards/speaker) from MSD, Gilead, AbbVie, BMS. DL: personal fees (advisory boards/grants) from BMS, AbbVie, Gilead, Janssen, MSD. CS: personal fees (speaker) from Gilead. HF: personal fees, advisory boards, presentations, congress invitations and/or trial participation for AbbVie, Gilead, MSD, Janssen, BMS, Roche. VL: personal fees (advisory boards/speakers' bureaus/consulting) from AbbVie, BMS, Gilead, Janssen, Merck. MB: personal fees (advisory boards/speaker) from MSD, Gilead, Janssen, Vertex, AbbVie, BMS, Novartis. DG: personal fees (advisory boards/speaker) from Servier, Intercept, AbbVie, Gilead, BMS, MSD, Janssen; grants from Janssen. IR: personal fees (advisory boards/symposia) from BMS, Janssen, Gilead, MSD, AbbVie. ENK: personal fees (speaker) from BMS, Gilead, Janssen, AbbVie; scientific committee participation for BMS. LF, RA, YB, AF and YZ: employees of BMS. JPB: personal fees/grants from BMS, Gilead, MSD, AbbVie. IHF, LDA, DBF and NB: no conflicts.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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