

## Retrospective Cohort Study

**Second-generation direct-acting-antiviral hepatitis C virus treatment: Efficacy, safety, and predictors of SVR12**

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**Abstract****AIM**

To gather data on the antiviral efficacy and safety of second generation direct acting antiviral (DAA) treatment with respect to sustained virological response (SVR) 12 wk after conclusion of treatment, and to determine predictors of SVR12 in this setting.

**METHODS**

Two hundred and sixty patients treated with SOF combination partners PR ( $n = 51$ ), R ( $n = 10$ ), SMV ( $n = 30$ ), DCV ( $n = 81$ ), LDV ( $n = 73$ ), or 3D ( $n = 15$ ).

144/260 were pre-treated, 89/260 had liver cirrhosis, 56/260 had portal hypertension with platelets < 100/nL, 25/260 had a MELD score  $\geq$  10 and 17/260 were post-liver transplantation patients. 194/260 had HCV GT1, 44/260 HCV GT3.

### RESULTS

Two hundred and forty/256 (93.7%) patients achieved SVR12 (mITT); 4/260 were lost to follow-up. SVR12 rates for subgroups were: 92% for SOF/DCV, 93% for each SOF/SMV, SOF/PR, 94% for SOF/LDV, 100% for 3D, 94% for pretreated, 87% for liver cirrhosis, 82% for patients with platelets < 100/nL, 88% post-liver transplantation, 95% for GT1a, 93% for GT1b, 90% for GT3, 100% for GT2, 4, and 6. 12 patients suffered from relapse, 6 prematurely discontinued treatment, of which 4 died. Negative predictors of SVR12 were a platelet count < 100/nL, MELD score  $\geq$  10 ( $P < 0.0001$ ), liver cirrhosis ( $P = 0.005$ ) at baseline. In Interferon-free treatment GT3 had significantly lower SVR rates than GT1 ( $P = 0.016$ ). Side effects were mild.

### CONCLUSION

Excellent SVR12 rates and the favorable side-effect profile of DAA-combination therapy can be well translated into "real-world". Patients with advanced liver disease, signs of portal hypertension, especially with platelets < 100/nL and patients with GT3 are in special need for further research efforts to overcome comparatively higher rates of virological failure.

**Key words:** Sofosbuvir; Simeprevir; Ledipasvir; Hepatitis C; Liver transplant; Sustained virological response; Liver cirrhosis; Side effects; Resistance; Daclatasvir

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**Core tip:** From 2014 on the second wave of direct acting antiviral agents was available for treatment of chronic hepatitis C infection. Due to the more heterogeneous character of patients in the "real world", the therapeutic performance of these new drugs outside randomized clinical trials is of interest. Therefore, in this monocentric retrospective cohort study, we analyzed the efficacy, safety, and predictors of sustained virological response 12 for treatment with combinations of second generation direct acting antivirals in a "real-world" setting.

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## INTRODUCTION

Chronic infection with Hepatitis C virus (HCV) is still one of the main causes for liver disease with a prevalence of 0.2%-2% in Western countries, while worldwide about 80 million people are threatened by HCV<sup>[1-4]</sup>. After many years of just moderate sustained viral response (SVR) rates of around 50%-60% through all genotypes (GT) under Interferon (IFN)-based treatment regimens<sup>[5-9]</sup>, in 2011 the first direct acting antiviral compounds (DAA), the protease inhibitors (PI) Telaprevir and Boceprevir had been approved for treatment of HCV GT1<sup>[10-14]</sup>. Beyond that, promising SVR results obtained in the clinical trials were shown to be achieved also in "real-world" settings<sup>[15,16]</sup>. However, treatment with first generation DAA was only subject to GT1 patients, and antiviral potency was counteracted by aggravated side-effects. For the second wave of DAA, diverse drug classes were developed: (1) polymerase-; (2) NS5A-, as well as (3) new protease inhibitors (PI). From early 2014 on, consecutively the first-in-class polymerase inhibitor Sofosbuvir (SOF), a second wave PI Simeprevir (SMV), the first-in-class NS5A inhibitor Daclatasvir (DCV), and another NS5A inhibitor Ledipasvir (LDV), were approved. Accordingly, for the first time, IFN-free treatments consisting of combinations of these DAA, with or without Ribavirin (R), were possible, showing impressive SVR rates and a superior side effect profile. From 2014 until 2015, SOF constituted the "backbone" of most combination treatments: in combination with R alone (SOF/R), with pegylated Interferon and R (SOF/PR), or combined with SMV (SOF/SMV), DCV (SOF/DCV), or LDV (SOF/LDV) with or without R. In 2015, this "monopoly" was tackled by the fixed combination of Dasabuvir, a non-nucleosidic polymerase inhibitor, with Ombitasvir, and Paritaprevir/r (3D).

Now, after more than two years since the approval of SOF and its combination partners, and a year after approval of the 3D regimen, we here summarize our experiences with these combination treatments being obtained in the "real-world" setting of a tertiary center. This retrospective analysis was conducted to gather data on the antiviral efficacy and safety of second generation DAA treatment with respect to sustained virological response 12 wk after conclusion of treatment (SVR12), and to determine predictors of SVR12 in this setting.

## MATERIALS AND METHODS

The clinical characteristics of our retrospective cohort are presented in Table 1. The study cohort includes all 260 consecutive patients, who were treated at our center with a DAA containing therapy between January 2014 and December 2015. Treatment decisions were

**Table 1 Characteristics of study cohort patients**

Demographics		
<i>n</i>		260
Age	(yr) <sup>1</sup>	53 (44-60)
Sex	Male/Female <i>n</i> (%)	157 (60)/103 (40)
Baseline viral characteristics		
Genotype 1a/1b/1x	<i>n</i> (%) / <i>n</i> (%) / <i>n</i> (%)	76 (29) / 115 (44) / 3(1)
Genotype 2/3	<i>n</i> (%) / <i>n</i> (%)	8 (3) / 44 (17)
Genotype 4/5/6	<i>n</i> (%) / <i>n</i> (%)	11 (4) / 1 (0.4) / 2 (0.8)
Baseline viral load	(IU/mL) <sup>1</sup>	1.33 Mio. (414.750-3.4 Mio.)
Baseline viral load ≥ 800.000 IU/mL	<i>n</i> (%)	169 (65)
Baseline viral load ≥ 6 Mio IU/mL	<i>n</i> (%)	28 (11)
Special populations		
LCi <sup>2</sup>	<i>n</i> (%)	89 (34)
Low platelets (≤ 100/nL)	<i>n</i> (%)	56 (22)
Post Liver Transplantation	<i>n</i> (%)	17 (7)
Patients ≥ 60 yr	<i>n</i> (%)	72 (28)
Patients with MELD score ≥ 10	<i>n</i> (%)	25 (10)
Treatment history		
Treatment experienced	<i>n</i> (%)	144 (55)
Treatment regimens [thereof liver cirrhosis <i>n</i> (%)]		
SOF PR	<i>n</i> (%) / LCi <i>n</i> (%)	51 (20) / 6 (12)
SOF R	<i>n</i> (%) / LCi <i>n</i> (%)	10 (4) / 4 (40)
SOF SMV	<i>n</i> (%) / LCi <i>n</i> (%) / R <i>n</i> (%)	30 (12) / 16 (53) / 15 (19)
SOF DCV	<i>n</i> (%) / LCi <i>n</i> (%) / R <i>n</i> (%)	81 (31) / 42 (52) / 12 (40)
SOF LDV	<i>n</i> (%) / LCi <i>n</i> (%) / R <i>n</i> (%)	73 (28) / 17 (23) / 16 (22)
3D	<i>n</i> (%) / LCi <i>n</i> (%) / R <i>n</i> (%)	15 (6) / 4 (27) / 6 (40)
Baseline clinical chemistry		
WBC	(/μL) <sup>1</sup>	5935 (4683-7670)
Hemoglobin	(g/dL) <sup>1</sup>	14.5 (13.1-15.6)
Platelets	(thousand/μL) <sup>1</sup>	174 (113-228)
Creatinine	(mg/dL) <sup>1</sup>	0.7 (0.6-0.8)
Total Bilirubin	(mg/dL) <sup>1</sup>	0.7 (0.5-1.0)
INR	INR <sup>1</sup>	1 (1-1)
ALT	IU/l <sup>1</sup>	67 (44-105)

<sup>1</sup>Data are presented as medians (interquartile ranges in parentheses);

<sup>2</sup>By liver histology, Fibrosan (> 12.5 kPa), or by clinical diagnosis (*e.g.*, esophageal varices, ascites, distinct ultrasound signs of portal hypertension or liver cirrhosis). 1x: Genotype 1, no subtype differentiable; LCi: Liver cirrhosis; MELD: Model of end stage liver disease; P: Pegylated Interferon; R: Ribavirin; SOF: Sofosbuvir; SMV: Simeprevir; LDV: Ledipasvir; DCV: Daclatasvir; 3D: Dasabuvir, Ombitasvir, and Paritaprevir/r; WBC: White blood cell count; INR: International normalized ratio; ALT: Alanine-aminotransferase.

based on antiviral activity against GT of respective DAA according to approval, severity of liver disease, comorbidities, approval of DAA at time-point of treatment start, and economic reasons.

If possible, IFN-free treatments were favored. Treatment of patients presenting hepatic impairment was postponed, if possible, until IFN-free regimens were available. 17 patients were treated in the context of post-liver transplantation, two of these with cholestatic recurrence of HCV after liver transplantation who were treated with SOF/DCV in a compassionate use program. Following the dates of approval of the

different DAA, patients were treated with SOF/R or SOF/PR respectively, when being started with treatment in early 2014, until later on additionally a SOF/SMV combination became available. From autumn 2014 on, patients were, if possible, treated with SOF/DCV, and again later on this year, patients could be treated also with SOF/LDV. From Early 2015 on, patients could also be treated with the 3D regimen. Proportions of different treatment regimens are shown in Table 1.

Baseline clinical chemistry is shown in Table 1. 13/260 patients had leukopenia (leukocyte count < 3000/μL), 56/260 patients presented with thrombopenia (platelet count < 100/nL). Transaminases were elevated in 223/260 patients (ALT > 35 IU/mL). Data of albumin levels were available only on an occasional basis.

Diagnosis of liver cirrhosis was based upon liver histology, Fibrosan (> 12.5 kPa), or clinical diagnosis (*e.g.*, ascites, esophageal varices, distinct sonographic signs of portal hypertension or liver cirrhosis). For assessment of severity of liver disease, we calculated the MELD score. In this retrospective analysis, Child Turcotte Pugh score or other assessment scores for severity of liver disease could not be calculated due to lack of data<sup>[17,18]</sup>. For retrospective identification of patients with possible portal hypertension, a threshold of 100 platelets/nL was assumed.

For virological analyses Roche CobasAmpliprep/Roche CobasTaqMan [Roche Diagnostics GmbH, Mannheim, Germany; lower limit of quantification (LLOQ) 15 IU/mL] was used.

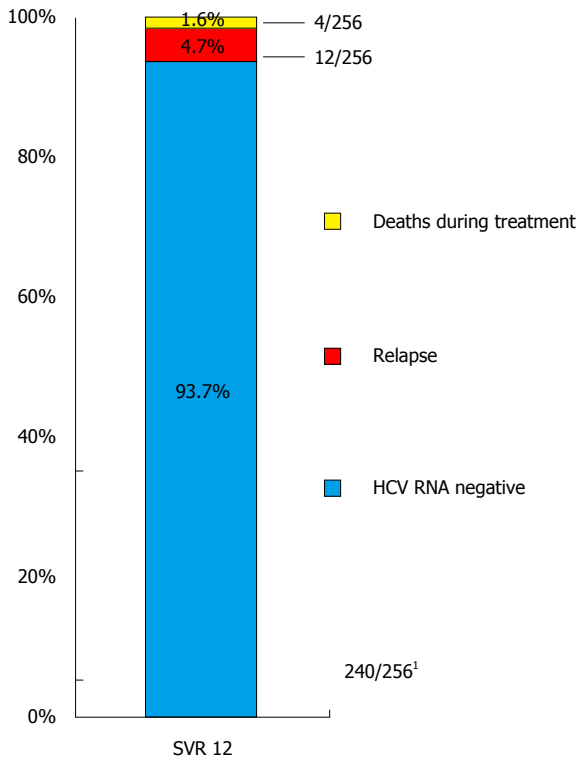
The institutional review board of the Medical Faculty of the University of Tübingen approved this retrospective analysis and waived the need for written informed consent because of the anonymous evaluation of patient data from patient records.

Data were statistically analyzed using Microsoft Office Excel, SPSS, and Graph Pad Prism. 4/260 patients were lost to follow-up. These patients were excluded from analysis [modified intention to treat analysis (mITT)].

## RESULTS

### Analysis of SVR12 rates

The overall SVR12 rate is shown in Figure 1 (93.7%; 240/256 patients mITT; of those, 2/256 patients discontinued treatment prematurely, but achieved SVR 12; 4/260 patients were lost to follow-up and were excluded from analysis. SVR12 rates according to GT, and diverse treatment regimens are shown in Figure 2. Additionally, SVR12 rates according to several baseline characteristics (sex, age, cirrhosis status, platelet count, MELD score, viral load, and treatment experienced patients) and early viral kinetics are shown in Table 2. SVR12 rates in different GT (1a, 1b, 2, 3, 4, and 6) ranged from 90%-100%. One additional patient with HCV GT 5 achieved SVR 12.



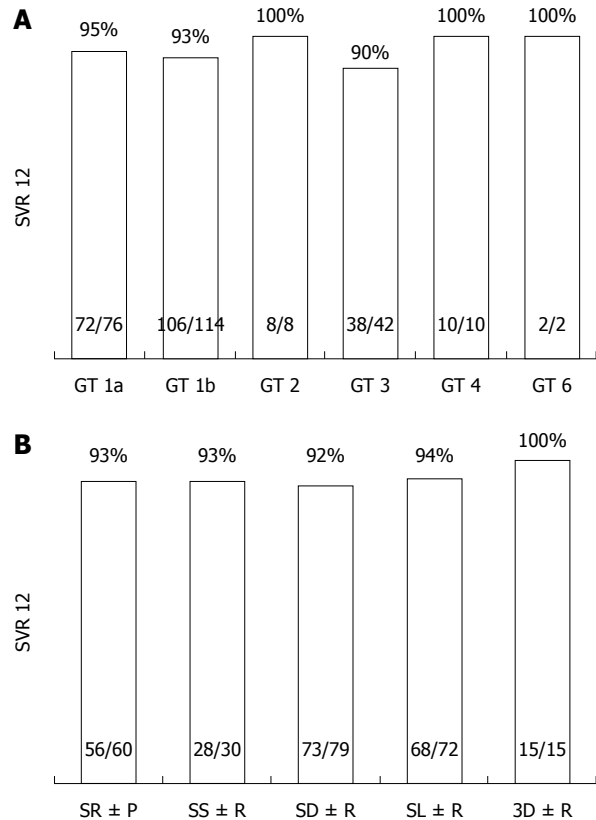
**Figure 1 Overall treatment outcome.** <sup>1</sup>Two hundred and sixty consecutive patients were treated with second generation direct acting antiviral (DAA) combinations; 14/260 patients lost to follow-up were not included in our analysis [modified intention-to-treat (mITT) analysis]. Additionally, 2 patients discontinued treatment prematurely, but achieved sustained virological response (SVR); accordingly these 2 patients also were counted as SVR12 patients.

Depending on different treatment regimens, SVR12 rates ranged from 92%-100%. Special subgroups of patients known to be "hard-to-treat" (patients post-liver transplantation ( $n = 17$ )), patients with liver cirrhosis ( $n = 89$ ), patients of older age ( $\geq 60$  years;  $n = 72$ ), and treatment experienced patients ( $n = 144$ ) achieved highly acceptable SVR12 rates in the range of 88%-95%. However, patients with low platelet count at baseline ( $< 100/\text{nL}$ ;  $n = 56$ ), and patients with a MELD score  $\geq 10$  at baseline ( $n = 25$ ) achieved SVR12 rates of 82%, and 72%, respectively.

### Predictors of SVR12

For evaluation of predictors of SVR12, see Table 2. Presence of liver cirrhosis ( $P = 0.005$ ), a platelet count  $< 100/\text{nL}$  ( $P < 0.0001$ ), and a MELD score  $\geq 10$  ( $P < 0.0001$ ) at baseline were significant negative predictors of SVR12 in our study cohort (univariate analysis). Multivariate analysis identified a platelet count  $< 100/\text{nL}$  ( $P = 0.031$ ), and a MELD score  $\geq 10$  ( $P < 0.0001$ ) at baseline as independent predictors for achievement of a diminished SVR12 rate (see Table 2 for details).

With respect to GT, in a "per-protocol" subgroup analysis of GT1 and GT3 patients strictly treated with IFN-free protocols, GT3 patients had a significantly lower SVR12 rate than GT1 patients ( $P = 0.016$ , univariate analysis).



**Figure 2 SVR12 rates with respect to GT (A), and diverse direct acting antiviral combinations (B, both modified intention-to-treat).** This mITT analysis excluded patients, who were lost to follow-up ( $n = 4$ ). Additionally, three GT1x patients and one GT 5 patient achieved SVR12. For further subgroup analyses according to baseline parameters see Table 2. 3D: Dasabuvir, Ombitasvir, and Paritaprevir/r; GT: Genotype; GT1x: Genotype 1, no subtype differentiable; P: Pegylated Interferon; R: Ribavirin; SR: Sofosbuvir, Ribavirin; SS: Sofosbuvir, Simeprevir; SL: Sofosbuvir, Ledipasvir; SD: Sofosbuvir, Daclatasvir; SVR: Sustained virological response.

However, in our cohort, treatment experience, sex, age, baseline viral load, and early virological kinetics were found not to be significant as predictors of SVR12.

### Virological failure

Virological failure was a rare event. No primary non-response or virological breakthrough occurred in our cohort. In addition, only 12 of the 256 patients (4.7%, mITT) suffered from virological relapse during follow-up (see Table 3 for baseline characteristics, treatment details, and resistance analysis of respective patients). One patient (No. 9 in Table 3) exhibiting a liver cirrhosis with Child-Turcotte-Pugh (CTP) stadium A suffered from relapse after SOF/PR. In this patient liver function deteriorated upon relapse to CTP stadium C, and therefore the patient had to be listed for liver transplantation (at a MELD score of 28). After having achieved an active listing status, treatment was initiated with SOF/DCV for 24 wk, leading to SVR12. During treatment, the liver function restored to CTP stadium A, and thus, the patient could be de-listed for liver transplantation again.



**Table 2 Predictive model of sustained virological response analyzed for all patients treated with second generation direct acting antiviracombination therapy (*n* = 256)**

	SVR 12 (n/N; %) <sup>2</sup>	Univariate analysis		Multivariate analysis	
		Odds ratio (95%CI)	Wald <i>P</i> value	Odds ratio (95%CI)	Wald <i>P</i> value
Viral kinetics					
RVR	143/152; 94%				
<i>vs</i> Non-RVR	83/89; 93%	1.149 (0.395, 3.341)	0.799		0.728
Baseline demographic parameters					
Fibrosis					
Liver Cirrhosis	76/87; 87%				
<i>vs</i> no Liver Cirrhosis	164/169; 97%	0.211 (0.071, 0.627)	0.005		0.290
Transplant Status					
LTx	15/17; 88%				
<i>vs</i> no LTx	225/239; 94%	0.467 (0.097, 2.246)	0.467		0.972
Sex					
Male	140/153; 92%				
<i>vs</i> female	100/103; 97%	0.329 (0.091, 1.184)	0.089		0.282
Age					
Patients ≥ 60 yr	68/71; 96%				
<i>vs</i> < 60 yr	172/185; 93%	0.999 (0.959, 1.04)	0.948		0.078
Baseline viral load					
High viral load (> 6 Mio IU/mL)	28/28; 100%				
<i>vs</i> low viral load (≤ 6 Mio IU/mL)	212/228; 93%	NA	0.998		0.251
Genotype					
1	180/192; 93%				
<i>vs</i> 3	38/42; 90%	1.606 (0.510, 5.060)	0.418		0.424
Genotype <sup>1</sup>					
1 IFN-free, per protocol	160/164; 98%				
<i>vs</i> 3 IFN-free, per protocol	16/20; 80%	5.000 (1.355, 18.45)	0.016		NA
Baseline platelet count					
Platelets ≤ 100/nL	45/55; 82%				
<i>vs</i> > 100/nL	195/201; 97%	0.138 (0.048, 0.401)	< 0.0001	0.24 (0.072, 0.88)	0.031
Baseline MELD ≥ 10					
MELD ≥ 10	18/25; 72%				
<i>vs</i> MELD < 10	222/231; 96%	0.104 (0.035, 0.313)	< 0.0001	0.117 (0.037, 0.373)	< 0.0001
Previous treatment response					
Pre-treated	133/142; 94%				
<i>vs</i> treatment-naive	107/114; 94%	0.967 (0.349, 2.681)	0.948		0.457

<sup>1</sup>This analysis excluded patients co-treated with IFN, and patients with premature discontinuation ("per protocol analysis"); <sup>2</sup>Number of patients who achieved SVR12 in category/total number in category. Univariate and multivariate models for prediction of SVR [*n* = 256, modified intention-to-treat (mITT) analysis] were used. This mITT analysis excluded patients, who were lost to follow-up (*n* = 4). Significant calculations (*P* < 0.05). RVR: Rapid viral response (hepatitis C virus RNA negative at treatment week 4); LTx: Liver transplantation; SVR: Sustained virological response; NA: Not available.

For GT1, 8/194 patients (4%) suffered from virological relapse, for GT3 a rate of 3/41 (9%) was found. All GT3 patients with relapse had advanced liver disease (cirrhosis or post-liver transplantation), while the GT1 cohort of relapsers was more heterogeneous. This emphasizes the new paradigm of GT3 (with advanced liver disease) being one of the harder-to-treat GT in the era of DAA (possibly due to an unintended "misfit design" of DAA with respect to this distinct genotype). In the group of IFN-free treated patients, the difference in SVR12 rates between GT1 and 3 was significant (*P* = 0.016, univariate analysis; Table 2).

In all patients with virological relapse after IFN-free DAA treatment resistance analysis was performed: Patients receiving a NS5A inhibitor always revealed NS5A-specific resistance associated variants (RAV) after relapse. Only one patient was detected with a NS5B-polymerase RAV (see Table 3 for details).

### Premature discontinuation of treatment

Altogether, 6 out of 256 (2.3%) patients discontinued treatment prematurely (see Table 3 for baseline characteristics, treatment details, and outcome). Four of those patients died during or shortly after discontinuation of treatment: two patients developed sepsis, one patient died from right-sided heart failure, and one patient died from cerebral hemorrhage. All these patients suffered from decompensated liver disease at baseline, two of those additionally were on immunosuppression due to prior organ transplantation (liver, and heart, respectively). Notably, these numbers are much too small to calculate significant associations between the respective causes of death and the DAA-class which had been used for HCV treatment, but the mere fact that 4 of our patients died emphasizes the need for treatment of those patients in an experienced tertiary center. However, these patients would have

**Table 3 Characteristics of patients, who died during treatment, discontinued treatment prematurely, or suffered from virological**

Age (yr)	Sex	BL viral load, IU/mL	GT	LCI	BL MELD	Previous treatment	Current treatment	Treatment duration	Cause for premature discontinuation	Outcome	RAV NS3 protease	RAV NS5A	RAV NS5B polymerase
Patients, who died during treatment, or discontinued treatment prematurely													
No. 1	63	male	1.41 Mio	1b	Yes	12	PR	12	Sepsis	death			
No. 2	66	male	1.69 Mio	1b	Yes, HITx	14	-	5	Intracranial bleeding	death			
No. 3	55	male	56200	1b	Yes, LTx	24	TVR/PR	14	Re-LTx, sepsis	death			
No. 4	49	male	157000	1a	Yes,	14	PR	8	Right-heart failure	death			
No. 5	79	female	5.85 Mio	1b	Yes	6	TVR/PR	10	Back-pain	SVR 24			
No. 6	55	male	396000	1a	Yes, TIPSS	10	PR	16	Hepatic encephalopathy	SVR 24			
Patients with relapse after end of treatment													
No. 7	54	male	10300	1a	Yes	8	PR	12			NA	NA	NA
No. 8	63	male	321000	1b	-	6	-	12			NA	NA	NA
No. 9	43	female	408000	1a	Yes	8	-	12			NA	NA	NA
No. 10	40	male	2.74 Mio	1b	-	6	PR	12			NA	NA	NA
No. 11	48	male	4.89 Mio	3a	No, LTx	11	PR	24			F43F/L	A30K	-
No. 12	56	female	1.38 Mio	3a	Yes	7	PR	24			-	Y93H	S282S/T
No. 13	38	male	3.39 Mio	1b	-	6	-	12			Q80K	L31M, Y93H	-
No. 14	52	male	2.47 Mio	3a	Yes	10	-	24			-	Y93H	-
No. 15	55	female	3.03 Mio	1a	-	6	TVR/PR	12			T54S, R155K	L31M/L	-
No. 16	49	male	8340	3	Yes	6	-	24			-	A30S	-
No. 17	52	male	239000	1b	Yes	6	-	12			T54S, V55I, Q80K	Q30E	-
No. 18	57	male	137 (on SOF/R)	1a	Yes, HCC	11	SOF/R	12			-	L31M, P58S, Y93C	-

BL: Baseline; GT: Genotype; HCC: Hepatocellular carcinoma; LCI: Liver cirrhosis; MELD: Model of end stage liver disease; P: Pegylated Interferon; R: Ribavirin; SOF: Sofosbuvir; SMV: Simeprevir; LDV: Ledipasvir; DCV: Daclatasvir; TVR: Telaprevir; RAV: Resistance associated variant; HITx: Heart transplantation; LTx: Liver transplantation; TIPSS: Transjugular portosystemic stent shunt; NA: Not available.

never been treated at time of IFN-containing regimens.

One patient discontinued due to back-pain after 10 wk of treatment, without contacting our center; nevertheless, this patient was found later on of having achieved SVR 24. Another patient with HCV GT1a, liver cirrhosis, and a transjugular portosystemic shunt (TIPSS) was discontinued after 4 mo of treatment due to several episodes of hepatic encephalopathy. Nevertheless, this patient also achieved SVR 24.

**Side effects**

One hundred and forty-seven/237 (62%) patients with data available for side effects reported side effects during treatment (depicted in detail in Table 4). In general, side effects were mild in intensity, thus, just one patient discontinued treatment prematurely due to a self-reported intolerance (*i.e.*, back-pain; Table 3). Overall, fatigue, headache, bone pain or joint pain, and myalgia were the most frequently reported side effects. As expected, the rate of side effects was found to differ significantly between patients with IFN-containing regimens versus patients with IFN-free treatment.

Hospital admissions were required during treatment with DAA-based regimens in 22 (8.6%) patients. Some of those patients had to be hospitalized twice or more. Reasons for hospitalization were: infections (*n* = 8; 4%), hepatic decompensation (*n* = 3; 1.5%), cardiovascular disease (*n* = 3), cholestatic hepatitis after liver transplantation (*n* = 2), treatment of hepatocellular carcinoma (*n* = 2), lumbago, vomitus, and diabetes insipidus, right upper quadrant pain (*n* = 1, each). Of

**Table 4** Patient self-reported side effects during treatment, and for comparison of self-reported side effects of PEG-interferon containing regimen and interferon-free treatment Fisher's exact test was used

Side effects	Overall <sup>1</sup>		PEG-IFN co-treatment <sup>2</sup>		IFN-free treatment <sup>3</sup>		P value
Fatigue	93	39.2%	26	54.2%	67	35.4%	0.020
Cephalgia	52	21.9%	9	18.8%	43	22.8%	0.697
Bone/joint pain/myalgia	38	16.0%	12	25.0%	26	13.8%	0.077
Nausea/vomiting	38	16.0%	14	29.2%	24	12.7%	0.008
							0.163
Insomnia	28	11.8%	16	33.3%	12	6.3%	< 0.0001
Vertigo	16	6.8%	6	12.5%	10	5.3%	0.102
Flu-like symptoms	14	5.9%	12	25.0%	2	1.1%	< 0.0001
Abdominal discomfort/pain	17	7.2%	3	6.3%	15	7.9%	1.000
Pruritus	18	7.6%	4	8.3%	13	6.9%	0.755
Diarrhea	13	5.5%	7	14.6%	6	3.2%	0.006
Any rash	14	5.9%	7	14.6%	7	3.7%	0.010
Anorexia	9	3.8%	4	8.3%	5	2.6%	0.085
Nervousness	7	3.0%	4	8.3%	3	1.6%	0.033
Depression/fear	5	2.1%	2	4.2%	3	1.6%	0.267
Dyspnoea	7	3.0%	4	8.3%	3	1.6%	0.030
Concentration weakness	4	1.7%	2	4.2%	2	1.1%	0.183
Visual changes	4	1.7%	1	2.1%	3	1.6%	1.000
Loss of hair	4	1.7%	1	2.1%	3	1.6%	1.000
Tachycardia/palpitations	2	0.8%	2	4.3%	0	0.0%	0.040
Meteorism	3	1.3%	0	0.0%	3	1.6%	1.000
Aggression	2	0.8%	2	4.2%	0	0.0%	0.040
Fever/chills	1	0.4%	1	2.1%	0	0.0%	0.200
Attacks of sweating	1	0.4%	1	2.1%	0	0.0%	0.200
Gingivitis	1	0.4%	0	0.0%	1	0.5%	1.000
Cough	1	0.4%	1	2.1%	0	0.0%	0.200
Neurological symptoms	1	0.4%	0	0.0%	1	0.7%	1.000

<sup>1</sup>Side effect reports were available in 237 of 260 patients; <sup>2</sup>In PEG-IFN co-treated patients ( $n = 51$ ), side effect reports were available in 48 patients; <sup>3</sup>In IFN-free treated patients ( $n = 209$ ), side effects reports were available in 189 patients. Significant calculations ( $P < 0.05$ ) are printed in bold. IFN: Interferon.

those hospitalized, 4 patients deceased: Two patients died from infectious complications, and two patients died from cardiovascular disease (right-heart failure, intracerebral bleeding, respectively; see above, and Table 3 for details).

One hundred and ten patients received R as part of their combination treatment. Of those, 5 patients had to reduce R dosage due to anemia (4.5%), and 2 due to renal impairment. 2 patients had to completely withdraw R, one due to pruritus, and the other due to hemolysis, respectively.

## DISCUSSION

This "real-world" monocentric retrospective cohort study analyzing safety, efficacy, and predictors of SVR12 of second generation DAA treatment shows impressive overall SVR rates (93.7%).

Due to the relatively small number of patients and the retrospective character of this study a comparison between subgroups according to DAA combination partners is only of limited significance.

Furthermore, due to the lesser tolerability and presumed lower activity of SOF/PR in patients with advanced liver disease, this treatment *a priori* was reserved in our hands to patients showing up with a

well-compensated liver function only.

The results in our heterogeneous cohort, containing meaningful fractions of hard-to-treat patients (liver cirrhosis, portal hypertension, post-liver transplantation) are similar to SVR rates of so far published study trials: our cohort of PR or R co-treated patients achieved a SVR rate of 93%, while in the NEUTRINO trial the cohort treated with SOF/PR achieved a SVR rate in previously untreated patients of 90%<sup>[19]</sup>, and the VA-real world cohort achieved SVR12 in 66.8%-79%<sup>[20]</sup>.

In other "real-world" analyses with SMV ± R as combination partners of SOF, SVR rates of 74.1%-84.2% were achieved<sup>[20-22]</sup>. In the OPTIMIST study, a phase III trial, a SVR12 rate of 97% in non-cirrhotic patients<sup>[23]</sup>, while in the OPTIMIST-2 study treating cirrhotic patients with SOF, SMV ± R, SVR 12 in 83% of patients was achieved<sup>[24]</sup>. However, in our cohort, with more than half of patients being patients with liver cirrhosis, we achieved a SVR rate of 93% with this combination of drugs.

For patients with SOF, DCV ± R as combination partners, SVR rates of 86%-93% have been reported<sup>[25]</sup>. In our cohort, we were in line with those results and could achieve a SVR rate of 92%, including two patients with recurrent cholestatic Hepatitis C post-liver

transplantation, one of those being a non-responder to a prior Telaprevir triple therapy being undertaken post-liver transplantation, and both decompensated at the beginning of treatment.

In previously treated and untreated patients with HCV, a combination of LDV ± R, and SOF led to SVR rates of 94%-99%<sup>[26-28]</sup>, which is in line with results of our cohort, in which we could register a SVR12 rate of 94%, while in another real-world analysis, SVR rates of 91.3%-92% were achieved<sup>[29]</sup>.

For our small group of 3D regimen-receiving patients, we could achieve SVR in 100%, while in the Phase III trials SVR rates of 91.8%-99.5% were observed<sup>[30,31]</sup>.

Thus, altogether, favorable SVR rates achieved in the randomized controlled clinical trials could be translated into the "real-world", and importantly, in our cohort; even extra hard-to-treat groups of patients exhibited favorable treatment outcomes (SVR12 post-liver transplantation: 88%, SVR12 in cirrhotic patients with platelets < 100/nL: 82%), which exceed results with former treatment options by far<sup>[15,32]</sup>.

Nevertheless, patients with liver cirrhosis show significantly lower response rates (87% with liver cirrhosis, 97% without;  $P = 0.005$ ), and especially those with advanced portal hypertension (platelets < 100/nL), or high MELD score ( $\geq 10$ ) show significantly lower SVR12 rates than patients without ( $P < 0.0001$ , uni- and multivariate analysis). These findings were also observed in other real world studies with low platelets, low albumin and liver cirrhosis as negative predictors of SVR in larger cohorts<sup>[21,33,34]</sup>. Thus, this subgroup of patients still resembles a group of patients in the "catch 22"-situation of being in the greatest need of treatment while showing the lowest response rates. Moreover, the whole drug class of HCV protease inhibitors (represented by SMV, and Paritaprevir/r) is not recommended for those patients (CTP B "plus") due to hepatotoxicity. Therefore, new strategies are needed to tackle this problem, *e.g.*, by implementation of screening programs to identify patients infected with HCV at an early stage of their liver disease, and more importantly by development of more potent agents in the near future. However, 4 patients were lost in our cohort. Even if not associated with anti-HCV medication, this emphasizes, that treatment of patients with advanced liver disease should remain in the hands of experienced tertiary centers even in times of "easy" treatment with second generation DAA.

In our cohort, results of early viral kinetics had no impact on prediction of SVR12, thus costly "in-between" measurements of HCV viral load possibly are expendable.

Previous treatment with PR may not play a role any more in treatment decisions, as in our cohort previous treatment was not identified as a negative predictor of SVR, as it was in the HCV-TARGET cohort<sup>[21]</sup>.

Most probably due to the favorable tolerability and low-toxicity profile of second generation DAA, and

the omission of pegylated Interferon, now also senior patients benefit from SOF-based DAA treatment on the same scale as younger patients do<sup>[21]</sup>.

Another subgroup of patients in need of further research efforts seems to be the one with GT3: Even though we could achieve a favorable overall SVR rate of 90%, at least in IFN-free treatment regimens, the SVR rates in a "per-protocol" analysis are significantly lower in GT3 patients than in GT1 (80% in GT3, 98% in GT1, respectively,  $P = 0.016$ ; univariate analysis), again with a special negative focus on patients with GT3 and concomitant advanced liver disease. Moreover, means are limited with respect to treatment of GT3 due to the insufficient antiviral activity of protease- and NS5A-inhibitors (except DCV) in this GT. However, new pangenotypic NS5A inhibitors like Velpatasvir or upcoming new pangenotypic protease inhibitors hopefully close that gap in the near future.

However, since DAA treatment forms RAVs in the viriome of patients, pretreatment with DAA of any generation has to be considered more and more in future treatment attempts after any prior exposure to DAA. All patients in our cohort, who suffered from virological relapse showed RAVs at time-point of relapse. Especially NS5A-RAVs are frequent due to the low resistance barrier of NS5A-inhibitors, as exemplified also in our "real-world" cohort. Since NS5A-RAVs lead to just minimal impairment of viral "fitness", unfortunately they are detectable for a long time in exposed patients<sup>[35]</sup>. While for some RAVs (like NS5A L31M, Y93H) clear associations between existence of RAV and virological failure exist, for others (like NS5A A30S) this association is not well established<sup>[35]</sup>. This may lead to confusion in case of a future re-treatment, if minor RAVs have been detected, and even more in case of a baseline test in treatment naïve patients. However, as the population of patients with relapse after DAA treatment grows, the need for controlled trials with new DAA-combinations (*e.g.*, pangenotypic protease inhibitor) for those patients to address this problem is obvious. Therefore, after virological relapse we recommend resistance testing for individualized adjustment of future DAA therapies.

In our retrospective analysis excellent SVR12 rates of second generation DAA could be translated from the large study trials into "real-world" scenarios. Patients with advanced liver disease, signs of portal hypertension, especially with platelets < 100/nL, or MELD  $\geq 10$ , and patients with GT3 are at relatively higher risk to suffer from virological failure and development of resistance associated variants after exposure to DAA. To overcome this unsolved problem, further research efforts are needed.

## COMMENTS

### Background

From 2014 on, successively the second wave of direct acting antiviral agents (Sofosbuvir, Daclatasvir, Simeprevir, Ledipasvir, Dasabuvir, Ombitasvir,



Paritaprevir/r) was available for treatment of chronic hepatitis C infection. In randomized clinical trials, superb rates of sustained virological response (SVR) 12 could be achieved.

### Research frontiers

Due to the more heterogeneous character of patients in the “real world”, the therapeutic performance of these new drugs outside randomized clinical trials is of interest. Therefore, in this monocentric retrospective cohort study, we analyzed the efficacy, safety, and predictors of SVR 12 for treatment with combinations of second generation direct acting antivirals in a “real-world” setting.

### Innovations and breakthroughs

In this retrospective study, similar SVR rates could be achieved compared to randomized clinical trials. However, certain subgroups of patients have significantly lower viral response rates: Significant negative predictors of SVR12 were a platelet count < 100/nL, a MELD score  $\geq 10$  (both  $P < 0.0001$ ), liver cirrhosis at baseline ( $P = 0.005$ ). Moreover, in Interferon-free treatment patients with HCV genotype 3 had significantly lower SVR rates than patients with HCV genotype 1 ( $P = 0.016$ ). In the future, these subgroups of patients should be more in the focus of research efforts to overcome lower rates of SVR.

### Applications

Current retrospective analysis shows that excellent SVR12 rates and the favorable side-effect profile of direct acting antiviral-combination therapy can be well translated into “real-world”.

### Peer-review

Good level-study to be ameliorated in the presentation of characteristics of cirrhotic patients that are an important part of the studied population.

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