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Real-life experience with first generation HCV protease inhibitor therapy in Germany: The prospective, non-interventional PAN cohort

HCV-Proteaseinhibitoren der ersten Generation im Praxisalltag: Ergebnisse der prospektiven, nicht-interventionellen PAN Kohorte

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Zusammenfassung

Hintergrund und Zielsetzungen: In der nicht-interventionellen Studie PAN, an der Patienten mit chronischer Hepatitis-C-Virus (HCV)-Infektion teilnahmen, wurde die Wirksamkeit und Sicherheit von Peginterferon alfa-2a (PEG-IFN) in Kombination mit Ribavirin (RBV) und den Proteasehemmern Boceprevir (BOC) oder Telaprevir (TVR) sowie die Einhaltung von Therapiealgorithmen durch niedergelassene Ärzte in Deutschland untersucht.

Methoden: Die Analyse schloss Patienten mit HCV-Genotyp 1-Infektion ein, die therapienaiv oder vorbehandelt (BOC oder TVR) waren. Erhoben wurden Daten zur Demografie, Vorbehandlung, virologischem Ansprechen, Sicherheit und Management der Patienten.

Ergebnisse: Insgesamt erreichten 58,1 % der 1087 Patienten ein dauerhaftes virologisches Ansprechen (SVR). Die Ansprechraten waren bei therapienaiven Patienten (BOC 55 %; TVR 63,4 %) und Relapsern (BOC 63,2 %; TVR 74,5 %) höher als bei Patienten mit Null-Response auf eine vorangegangene Therapie (BOC 14,3 %; TVR 25 %). Das unerwünschte Ereignis, über das am häufigsten berichtet wurde, war Erschöpfung (60,6 %); 45,8 % der Patienten hatten Hämoglobinwerte < 10 g/dL. Die SVR-Raten waren bei Patienten mit Zirrhose niedriger als bei Patienten ohne Zirrhose (42,9 % vs. 60,7 %), die Raten schwerer unerwünschter Ereignisse (SUE) (16,7 % vs. 8,6 %) und Therapieabbruchraten höher (44,6 % vs. 25,2 %). Ungefähr 70 % der Patienten wurden gemäß den responsegesteuerten Therapiealgorithmen behandelt, bei 11 % bzw. 10 % der Patienten (BOC/TVR) wurde die Behandlung unnötig verlängert, bei 19 % bzw. 7 % (BOC/TVR) unangemessen verkürzt.

Schlussfolgerungen: Die Wirksamkeit und Sicherheit der BOC- und TVR-haltigen Triple-Therapie in dieser großen „Real-World"-Kohorte war weitgehend vergleichbar mit den Ergebnissen der

Abstract

Background and Aims: The efficacy and safety of peginterferon alfa-2a (PEG-IFN) plus ribavirin (RBV) and either boceprevir (BOC) or telaprevir (TVR), and physician adherence to treatment algorithms were evaluated in patients included in an ongoing non-interventional study (PAN) enrolling adults with chronic hepatitis C virus (HCV) infection managed in German office-based practices.

Methods: The analysis included HCV genotype 1-infected, treatment-naïve and treatment-experienced patients treated with BOC or TVR. Demographic, treatment history, virological response, safety, and patient management data were collected.

Results: Of a total 1087 patients, 58.1 % achieved sustained virological responses (SVR). Response rates were higher in treatment-naïve (BOC 55 %; TVR 63.4 %) and prior relapse patients (BOC 63.2 %; TVR 74.5 %) versus previous null-responders (BOC 14.3 %; TVR 25 %). The most commonly reported adverse event overall was fatigue (60.6 %); 45.8 % patients experienced hemoglobin < 10 g/dL. Patients with cirrhosis had lower rates of SVR versus those without (42.9 % vs. 60.7 %, respectively), and had a higher incidence of serious adverse events (SAEs) (16.7 % vs. 8.6 %, respectively) and treatment discontinuation (44.6 % vs. 25.2 %, respectively). According to recommended response-guided treatment algorithms, about 70 % of patients were managed appropriately, 11/10 % (BOC/TVR) received unnecessarily extended therapy, and 19/7 % (BOC/TVR) received inappropriately shortened therapy.

Conclusions: The efficacy and safety of BOC- and TVR-based triple therapy in this large, "real-world" cohort were largely comparable to that reported in pivotal clinical trials, although SVR rates were lower overall. Recommended futility or treatment extension rules were violated in a sub-

Zulassungsstudien, obwohl die SVR-Raten insgesamt niedriger waren. Bei einem beträchtlichen Teil der Patienten wurden die empfohlenen Stoppregeln oder Kriterien für eine Therapieverlängerung nicht beachtet, was potenzielle Auswirkungen auf Therapieansprechen, unerwünschte Ereignisse und Behandlungskosten hat.

stantial proportion of patients with potential implications for response, adverse events and costs.

Introduction

Hepatitis C virus (HCV) infection is a significant global burden with wide-ranging individual and socioeconomic impact. In Europe, the prevalence of chronic HCV infection is estimated to range from < 0.5 % in many Northern European countries to > 3 % in Romania and rural areas in Greece, Italy and Russia [1]. The predominant HCV genotype in Europe is genotype 1, responsible for more than 50 % of all infections. For over a decade, the standard of care for chronic HCV infection was treatment with peginterferon alfa plus ribavirin (PEG-IFN+RBV). However, patients with HCV genotype 1 infection respond less well to therapy with PEG-IFN+RBV compared with other genotypes, and those who fail to achieve sustained virological response (SVR) with PEG-IFN+RBV respond poorly to re-treatment with the same regimen [2 – 4]. The introduction of triple therapy combining PEG-IFN+RBV with the first-generation HCV protease inhibitors boceprevir (BOC) or telaprevir (TVR) has improved the response in genotype 1 patients, resulting in SVR rates of up to 75 % in treatment-naïve patients [5, 6], 75 – 88 % for prior PEG-IFN+RBV relapsers, 50 – 55 % for prior partial non-responders and 30 % for non-responders [7, 8]. However, the use of these drugs as a third agent is challenging in routine practice. Triple therapy results in a substantial increase in adverse events compared to dual therapy, particularly an increase in the incidence and severity of anemia and skin reactions. In particular patients with cirrhosis experience a high incidence of serious adverse events (SAEs), including liver decompensation, sepsis and death. This limits the use of triple therapy in this group of patients with a high need for viral eradication [9]. Based on the results of pivotal clinical trials, somewhat complex treatment algorithms and stopping/futility rules are recommended for response-guided therapy (RGT). Good adherence to RGT is important, not only to maximize the chances of SVR, but also to minimize unnecessary exposure to a potentially harmful treatment. In addition the development of treatment-resistant viral mutations may be reduced by stopping rules due to early discontinuation of ineffective therapy.

The next generations of direct acting antivirals (DAAs) offer simpler and finally interferon-free, all-oral treatment regimens with markedly improved tolerability and shorter treatment durations [10 – 15]. The benefits of these newer treatment options and the poor side effect profile of BOC and TVR are reflected in recent treatment guidelines, which no longer recommend BOC and TVR for the treatment of patients with HCV genotype 1 infection where more efficacious and better-tolerated options are available [16, 17]. As such, since the study was conducted, BOC and TVR are no longer routinely used in Germany. However, pricing strategies and local regulatory conditions mean that triple therapy with BOC or TVR will remain a treatment option for genotype 1 patients in many countries. Real world data therefore remain of interest as additional information to clinical trial data which represent a more selected patient population and controlled setting.

The PAN study is an ongoing multicenter, non-interventional database enrolling adults with detectable HCV RNA managed in office-based practices in Germany. In the current study we analyzed data from patients included in the PAN database who received triple therapy with BOC or TVR. The aim of the current analysis was to establish the efficacy and safety of these regimens in routine practice, and also to investigate specific aspects of care, including physician adherence to treatment algorithms.

Patients and Methods

PAN is an ongoing, open-label, multicenter, non-interventional study of adults with detectable HCV RNA conducted by the Association of German Gastroenterologists in office-based practices (Berufsverband Niedergelassener Gastroenterologen Deutschlands e. V., bng) in collaboration with Roche Pharma AG, Germany. Outpatients treated in office-based practices or hospital clinics were included.

The decision to initiate treatment and choice of treatment regimen was entirely at the discretion of the physician. The analysis included treatment-naïve and treatment-experienced patients with HCV genotype 1 monoinfection who received PEG-IFN alfa-2a + RBV (Roche Pharma, Grenzach-Wyhlen, Germany) plus either BOC (Merck Sharp & Dohme, Haar, Germany) or TVR (Janssen-Cilag, Neuss, Germany). Patients who initiated treatment prior to May 31st, 2012, with available 10 – 12 weeks post-treatment data and completed follow-up documentation or fully documented early treatment discontinuation were eligible. Data cut-off for the current analysis was August 1st, 2013 (study is ongoing). There were no other specified inclusion or exclusion criteria for the analysis. Data collection was performed via an online electronic case report form. Baseline data included age, sex, weight, height, duration of and risk factors for infection, prior antiviral treatment, clinical symptoms, liver histology, HCV genotype, HCV RNA, and concomitant diseases. Liver fibrosis was estimated using the non-invasive FIB-4 test which combines standard biochemical values (platelets, alanine aminotransferases) and age according to the formula originally described by Sterling et al. [18], where a score of > 3.25 correlates with severe fibrosis/cirrhosis. Virological response was defined as follows: rapid virological response (RVR) HCV RNA undetectable or < 10 IU/mL at week 4; extended RVR (eRVR) HCV RNA undetectable or < 10 IU/mL at week 8 and week 24 (BOC) or week 4 and week 12 (TVR); SVR12 was defined as undetectable HCV RNA at least 10 weeks after end of therapy. This definition (i. e. at least 10 weeks after end of therapy) was used because the timing of patient visits was not specified and thus some patients may not have had a physician visit at exactly 12 weeks.

Ethics approval

All data taken from the PAN cohort were pseudonymized; informed consent was obtained from all participating patients. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by central and local ethic committees (Ethikkommission der Ärztekammer

Westfalen-Lippe, Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster).

Statistics

The statistical analysis was primarily descriptive to reflect the non-interventional character. Summary statistics or frequencies and proportions were assessed depending on the scale level of the data. For the continuous variables age and baseline HCV RNA receiver operating characteristic analyses estimated the best cut-off point for SVR. The cut-off points found for the continuous variables were used for generating the corresponding categorical variables. Associations of various factors with SVR were first analyzed using univariate regression analyses. All variables reaching a $p < 0.05$ in the univariate analyses were entered in a multiple logistic regression analysis including odds ratio and 95 % confidence interval.

All statistical analyses were based on 2-sided hypothesis tests. Analyses were carried out using SPSS 12.0.2 (SPSS Inc., Chicago, Illinois, USA) and Testimate, version 6.4.27 (Institute for Data Analysis and Study Planning, Gauting/Munich, Germany).

Results

Patient disposition is shown in **Fig. 1**. From a total of 8193 patients included in the PAN database, 1087 fulfilled the inclusion criteria and were included in the final data analyses. Baseline characteristics are shown in **Table 1**. The majority of patients were male and Caucasian. Treatment-experienced patients were older, and had higher rates of cirrhosis compared with treatment-naïve patients; relapse was the most commonly reported reason for failure of previous therapy. Overall, 168 patients (15.5 %) had liver cirrhosis. Baseline data were similar between patients without cirrhosis and those with cirrhosis, with the exception of age, gender, and incidence of diabetes.

Efficacy

Overall 632 (58.1 %) patients achieved SVR 12. As expected the highest rates of response were seen in treatment-naïve and prior relapse patients, and the lowest in prior null responders (**Fig. 2a, b**). Reflecting the 'real-life' nature of the PAN cohort, a high proportion of treatment-experienced patients did not have detailed information regarding their response to previous

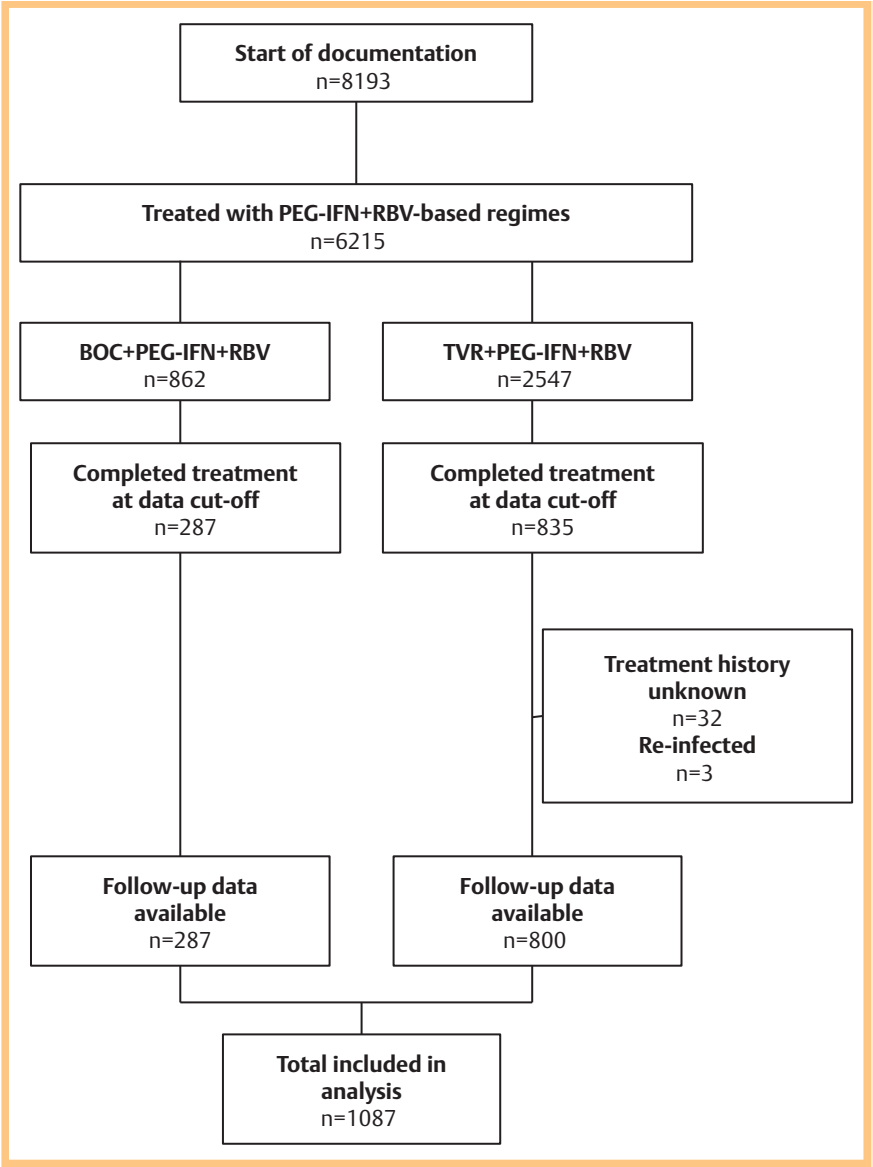

Fig. 1 Patient disposition.

Table 1 Baseline characteristics.

	BOC + PEG-IFN + RBV		TVR + PEG-IFN + RBV		total (n = 1087)
	treatment-naïve (n = 140)	treatment-experienced (n = 147)	treatment-naïve (n = 273)	treatment-experienced (n = 527)	
age (years), mean ± SD	47.3 ± 10.2	51.8 ± 10.2	46.5 ± 12.0	50.7 ± 10.7	49.3 ± 11.1
male, n (%)	86 (61.4)	76 (51.7)	162 (59.3)	337 (63.9)	661 (60.8)
caucasian, n (%)	132 (94.3)	143 (97.3)	265 (97.1)	514 (97.5)	1054 (97.0)
body mass index (kg/m^3), mean ± SD	29.6 ± 5.4	27.6 ± 5.2	25.7 ± 4.1	26.3 ± 4.2	26.4 ± 4.5
cirrhosis[1], n (%)	14 (10.0)	21 (14.3)	21 (7.7)	112(21.3)	168 (15.5)
diabetes mellitus, n (%)	7 (5.0)	19 (12.9)	12 (4.4)	44 (8.3)	82 (7.5)
genotype 1 subtype, n (%)					
1a	45 (32.1)	44 (29.9)	86 (31.5)	148 (28.1)	323 (29.7)
1b	67 (47.9)	79 (53.8)	134 (49.1)	260 (49.3)	540 (49.7)
other/unknown	28 (20.0)	24 (16.3)	53 (20.4)	119 (22.6)	224 (20.6)
ALT, n/N[2, 3] (%)					
normal	25/124 (20.2)	36/135 (26.7)	39 (15.9)	105 (21.7)	205 (20.7)
> 3 × ULN	24/124 (19.4)	22/135 (16.3)	51/245 (20.8)	104/484 (21.5)	210/988 (20.3)
FIB-4 ≥ 3.25, n/N[2] (%)	12/116 (10.3)	20/118 (16.9)	33/230 (14.3)	90/454 (19.8)	155/ 918 (16.9)
IL28B genotype, n (%)					
CC	14 (10.0)	8 (5.4)	19 (7.0)	21 (4.0)	62 (5.7)
CT	22 (15.7)	17 (11.6)	32 (11.7)	68 (12.9)	139 (12.8)
TT	2 (2.1)	8 (5.4)	16 (5.9)	25 (4.7)	52 (4.8)
not done	101 (72.1)	114 (77.6)	206 (75.5)	413 (78.4)	834 (76.7)
HCV RNA (log_{10} IU/mL), mean ± SD	6.0 ± 0.9	6.0 ± 1.1	6.0 ± 0.8	6.0 ± 0.8	6.0 ± 0.8
HCV RNA > 400,000 IU/mL, n/N[2] (%)	103/135 (76.3)	103/144 (71.5)	207/271 (76.4)	386/516 (74.8)	799/1066 (75.0)
treatment history, n (%)					
treatment-naïve	140 (100)	0	273 (100)	0	413 (38.0)
non response[4]	0	7 (4.8)	0	48 (9.1)	55 (5.1)
partial response[5]	0	17 (11.6)	0	81 (15.4)	98 (9.0)
relapse	0	76 (51.7)	0	274 (52.0)	350 (32.2)
undefined viral non-response	0	36 (24.5)	0	124 (23.5)	160 (14.7)
viral treatment history unknown	0	11 (7.4)	0	0	11 (1.0)

[1] Defined by at least one of the following criteria: biopsy, clinical appearance, sonography, elastography.
[2] Patients with available data.
[3] ULN: male 50 IU/L, female 35 IU/L.
[4] Patients who failed to achieve a greater than 2 log drop in HCV-RNA levels after 12 weeks of treatment.
[5] Patients who achieved at least a 2 log drop in HCV RNA during treatment but who never achieved a viral load under the limit of detection. (SD = standard deviation; ULN = upper limit of normal).

therapy ("undefined non-response"). In these groups, SVR rates were 38.9 % and 36.3 % in BOC- and TVR-treated patients, respectively.

Of the 166 patients in the study with cirrhosis, 72 (42.9 %) achieved SVR12, compared with 551/907 (60.7 %) of patients without cirrhosis. SVR12 rates were comparable in both treatment-naïve and treatment-experienced patients with cirrhosis, irrespective of treatment group (**Fig. 2c**).

Safety

Commonly reported adverse events are shown in **Table 2**. In general, adverse events were similar between treatment-naïve and treatment-experienced patients. Overall, 47.7 % of BOC-treated and 45.6 % of TVR-treated patients experienced laboratory-assessed anemia (hemoglobin levels < 10 g/dL), with similar rates in treatment-naïve and experienced patients.

In BOC-treated patients, SAEs reported by more than one patient were anemia (n = 6; 2.1 %) and newly diagnosed esophageal varices (n = 2; 0.7 %). In TVR-treated patients, SAEs reported by more than one patient were anemia (n = 17; 2.1 %), rash (n = 6; 0.75 %), pneumonia (n = 4; 0.5 %), pyrexia (n = 2; 0.25 %), fatigue (n = 2; 0.25 %), gastroenteritis (n = 2; 0.25 %), ascites (n = 2; 0.25 %), febrile infection (n = 2; 0.25 %) and hepatic failure (n = 2; 0.25 %).

No renal-related SAEs were reported. Increased blood creatinine was reported in two patients; one treatment-naïve without cirrhosis at baseline, and one treatment-experienced patient, both treated with TVR. Overall, the estimated glomerular filtration rates (eGFR; Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) remained stable. Of those patients with eGFR > 60 mL/min at baseline with available data, 6.9 % (4.7 % BOC; 7.6 % TVR) experienced a decline in eGFR to ≤ 60 mL/min at study week 12. Two patients (one each in the BOC and TVR groups) had a decline in eGFR to ≤ 30 mL/min. Overall, by end-of treatment and at follow-up, 97.5 % and 98.4 %, respectively, had eGFR > 60 mL/min. Changes in eGFR for those patients who showed an on-treatment decline to < 60 mL/min are shown in **Fig 3**.

Dose modifications of PEG-IFN occurred in 15 % of BOC-treated patients and 7.6 % of TVR-treated patients. Dose modifications of RBV occurred in 33.8 % of BOC-treated patients and 25.7 % of TVR-treated patients.

Three patients (0.3 %) died during the course of the study: two treatment-naïve patients treated with BOC (intravenous drug user found dead, cause of death unknown; hepatorenal syndrome associated with sepsis, considered possibly related to RBV and citalopram); one treatment-experienced patient treated

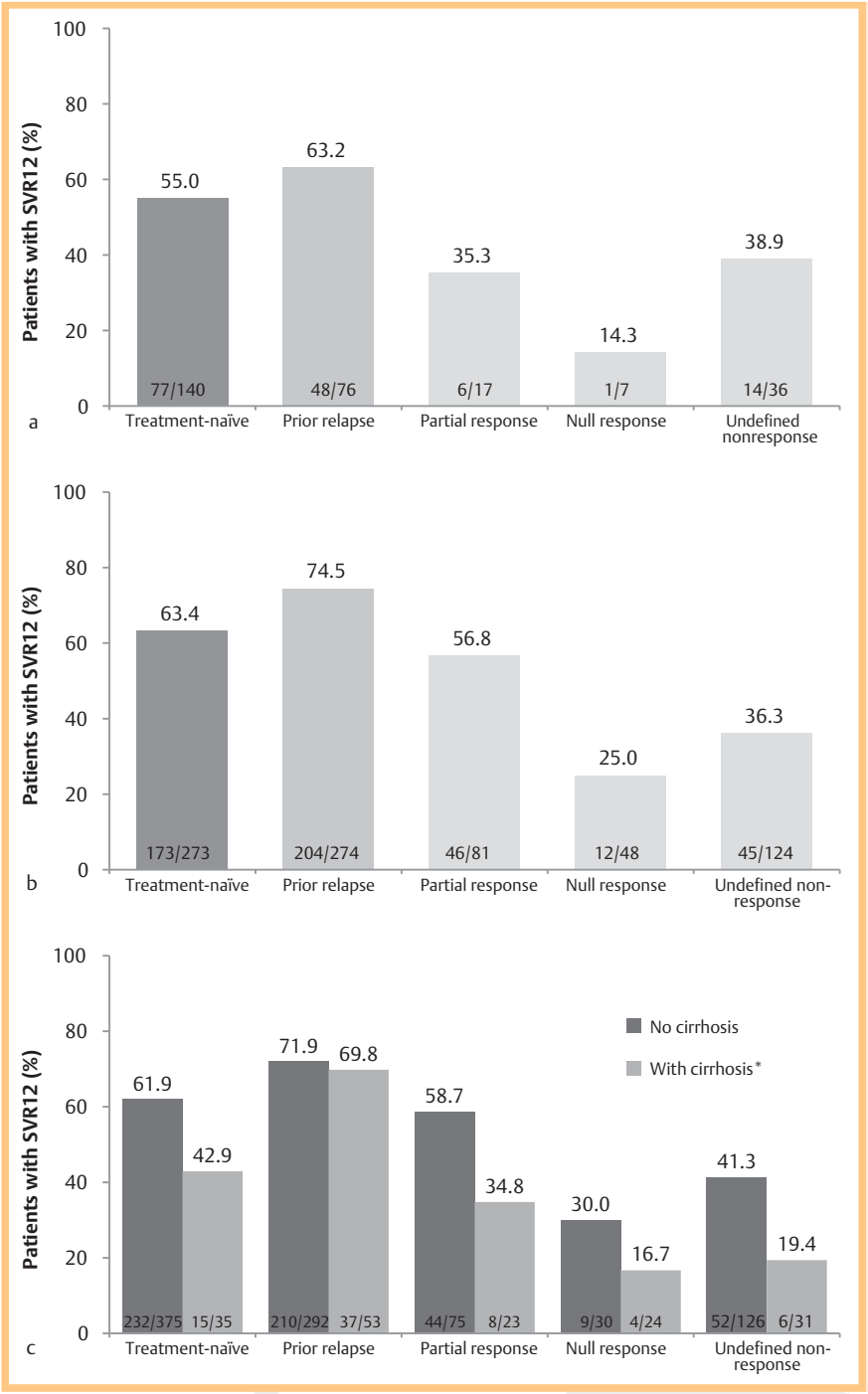

Fig. 2 SVR12 rates according to prior treatment history and presence of cirrhosis. **a** SVR12 in BOC-treated patients according to prior treatment history. **b** SVR12 in TVR-treated patients according to prior treatment history. **c** SVR12 in BOC-treated patients with and without cirrhosis. Treatment-experienced cohorts include only those patients with specified prior treatment response (* for 2 patients: unknown treatment history; BOC, boceprevir; SVR, sustained virological response; TVR, telaprevir).

with TVR (intravenous drug user, cause of death sepsis, possibly related to PEG-IFN, RBV and ceftriaxone).

Overall, rates of pruritus, anemia, diarrhea and insomnia were higher in patients with cirrhosis (**Table 3**). SAEs were markedly more common in patients with cirrhosis. Anemia was the most commonly reported SAE in patients with cirrhosis, although overall rates were similar to those reported in patients without cirrhosis (1.8 % vs. 2.2 %, respectively). However, the proportion of cirrhotic patients with hemoglobin < 8.5 g/dL was twice as high in those treated with BOC compared with non-cirrhotic patients (22.9 % vs. 10.2 %) and was slightly higher in TVR-treated patients with cirrhosis compared with those without (16.0 % vs. 14.4 %, respectively), although patient numbers were small.

More patients with cirrhosis compared with patients without cirrhosis required dose modification of RBV (BOC treated: 48.6 % and 32.1 %, respectively; TVR-treated: 30.8 % and 24.5 %, respectively) and/or PEG-IFN (BOC treated: 25.7 % and 13.8 %, respectively; TVR-treated: 13.5 % and 6.4 %, respectively).

Treatment discontinuation

In total, 306 (28.2 %) patients discontinued treatment (BOC: treatment-naïve 22.1 %, treatment-experienced 28.6 %; TVR: treatment-naïve 25.6 %, treatment-experienced 30.9 %). The most common reasons for discontinuation were lack of response and patient request in treatment-naïve patients, and lack of re-

Table 2 Adverse events, serious adverse events and treatment discontinuations, treatment-naïve vs. treatment-experienced patients, n (%).

	BOC + PEG-IFN + RBV			TVR + PEG-IFN + RBV		
	treatment-naïve (n = 140)	treatment-experienced (n = 147)	overall (n = 287)	treatment-naïve (n = 273)	treatment-experienced (n = 527)	overall (n = 800)
any AE	122 (87.1)	135 (91.8)	257 (89.5)	244 (89.4)	476 (90.3)	720 (90.0)
SAEs	17 (12.1)	16 (10.9)	33 (11.5)	24 (8.8)	50 (9.5)	74 (9.3)
discontinuations due to AEs	5 (3.6)	10 (6.8)	15 (5.2)	21 (7.7)	33 (6.3)	54 (6.8)
deaths	2 (1.4)	0	2 (0.7)	1 (0.4)	0	1 (0.1)
adverse events[1]						
fatigue	84 (60.0)	97 (66.0)	181 (63.1)	163 (59.7)	315 (59.8)	478 (59.8)
skin disorder	38 (27.1)	36 (24.5)	74 (25.8)	79 (28.9)	165 (31.3)	244 (30.5)
pruritis	25 (17.9)	34 (23.1)	59 (20.6)	84 (30.8)	155 (29.4)	239 (29.9)
nausea	37 (26.4)	39 (26.5)	76 (26.5)	82 (30.0)	134 (25.4)	216 (27.0)
anemia	31 (22.1)	23 (15.6)	54 (18.8)	65 (23.8)	118 (22.4)	183 (22.9)
headache	39 (27.9)	39 (26.5)	78 (27.2)	45 (16.5)	84 (15.9)	129 (16.1)
arthralgia	21 (15.0)	34 (23.1)	55 (19.2)	46 (16.8)	74 (14.0)	120 (15.0)
insomnia	20 (14.3)	27 (18.4)	47 (16.4)	37 (13.6)	73 (13.9)	110 (13.8)
depressed mood	23 (16.4)	25 (17.0)	48 (16.7)	40 (14.7)	62 (11.8)	102 (12.3)
dysgeusia	27 (19.3)	41 (27.9)	68 (23.7)	22 (8.1)	51 (9.7)	73 (9.1)
myalgia	23 (16.4)	33 (22.4)	56 (19.5)	32 (11.7)	47 (8.9)	79 (9.9)
pyrexia	20 (14.3)	18 (12.2)	38 (13.2)	38 (13.9)	50 (9.5)	88 (11.0)
irritability	21 (15.0)	19 (12.9)	40 (13.9)	27 (9.9)	37 (7.0)	64 (8.0)
alopecia	15 (10.7)	22 (15.0)	37 (12.9)	36 (13.2)	33 (6.3)	69 (8.6)
diarrhea	11 (7.9)	17 (11.6)	28 (9.8)	25 (9.2)	44 (8.3)	69 (8.6)
decreased hemoglobin						
< 8.5 g/dL	14 (10.0)	20 (13.6)	34 (11.8)	42 (15.6)	75 (14.3)	117 (14.8)
≥ 8.5–< 10 g/dL	54 (38.6)	49 (33.3)	103 (35.9)	86 (32.0)	162 (31.0)	248 (31.0)

[1] Reported in > 10 % of patients in any treatment group (AEs, adverse events; SAEs, serious adverse events).

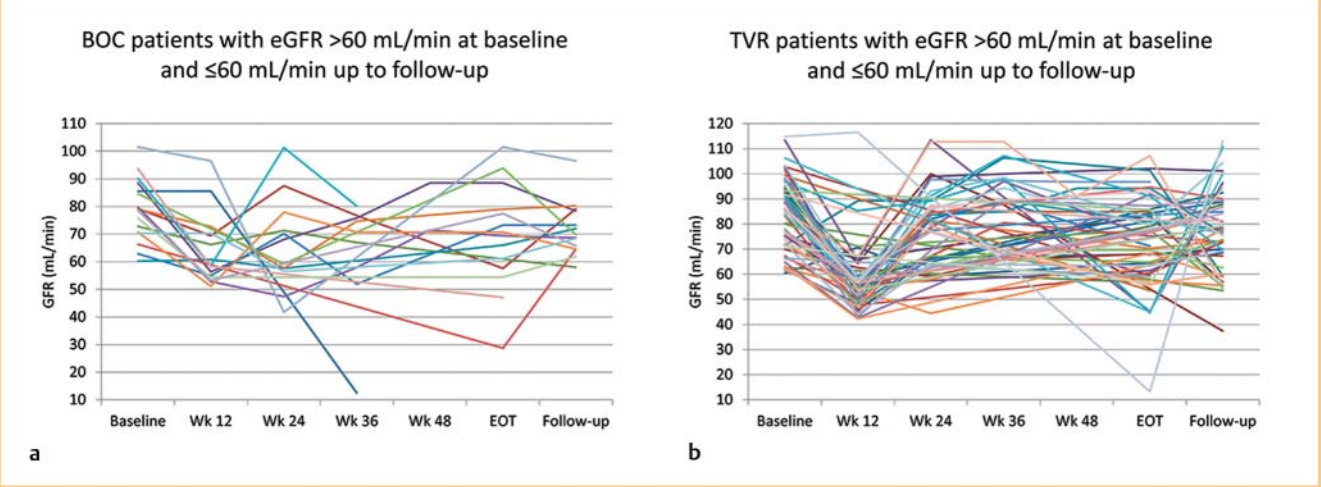

Fig. 3 Estimated glomerular filtration rate (eGFR) in patients with eGFR > 60 mL/min at baseline who experienced eGFR ≤ 60 mL/min at any time during the study period. **a** BOC-treated patients, **b** TVR-treated patient

sponse (and adverse events in treatment-experienced patients (**Table 4**).

Rates of discontinuation were higher in patients with cirrhosis compared with those without (44.6 % vs. 25.2 %, respectively overall), predominantly due to lack of response (overall: 25.6 % vs. 12.8 %; BOC 20.0 % vs. 11.8 %; TVR 27.1 % vs. 13.2 %, respectively). Adverse events led to discontinuation in 10.7 % of patients with cirrhosis and 5.6 % of patients without cirrhosis. Rates of discontinuation due to adverse events were similar in both groups treated with BOC (5.7 % and 5.3 %, respectively). In TVR-treated patients, rates were higher in patients with cirrhosis compared with patients without cirrhosis (12.0 % and 5.7 %, respectively).

Patient management

BOC-treated patients: The analysis was restricted to 140 treatment-naïve genotype 1 patients who received BOC plus PEG-IFN +RBV, completed 24 – 28 weeks of treatment (including the 4 week lead-in phase), and who had adequate documentation.

For BOC-based triple therapy, patients received a 4 week lead-in treatment with PEG-IFN + RBV prior to the addition of BOC. The recommended treatment duration for BOC-based triple therapy

	BOC + PEG-IFN + RBV		TVR + PEG-IFN + RBV	
	no cirrhosis (n = 246)	cirrhosis (n = 35)	no cirrhosis (n = 661)	cirrhosis (n = 133)
any AE	219 (89.0)	33 (94.3)	590 (89.3)	124 (93.2)
SAEs	25 (10.2)	7 (20.0)	53 (8.0)	21 (15.8)
discontinuations due to AEs	13 (5.3)	2 (5.7)	38 (5.7)	16 (12.0)
adverse events[1]				
fatigue	155 (63.0)	22 (62.9)	390 (59.0)	84 (63.2)
skin disorder	64 (26.0)	10 (28.6)	205 (31.0)	36 (27.1)
pruritis	47 (19.1)	9 (25.7)	188 (28.4)	48 (36.1)
nausea	62 (25.2)	12 (34.3)	180 (27.2)	33 (24.8)
anemia	45 (18.3)	9 (25.7)	143 (21.6)	38 (28.6)
headache	64 (26.0)	12 (34.3)	115 (17.4)	14 (10.5)
arthralgia	46 (18.7)	7 (20.0)	101 (15.3)	17 (12.8)
insomnia	33 (13.4)	12 (34.3)	86 (13.0)	24 (18.0)
depressed mood	43 (17.5)	4 (11.4)	88 (13.3)	13 (9.8)
dysgeusia	63 (25.6)	4 (11.4)	62 (9.4)	10 (7.5)
myalgia	47 (19.1)	7 (20.0)	64 (9.7)	15 (11.3)
pyrexia	31 (12.6)	5 (14.3)	68 (10.3)	19 (14.3)
irritability	33 (13.4)	6 (17.1)	53 (8.0)	11 (8.3)
alopecia	28 (11.4)	7 (20.0)	65 (9.8)	3 (2.3)
diarrhea	21 (8.5)	6 (17.1)	53 (8.0)	16 (12.0)
decreased hemoglobin				
< 8.5 g/dL	25 (10.2)	8 (22.9)	94 (14.4)	21 (16.0)
≥ 8.5–< 10 g/dL	90 (36.6)	11 (31.4)	193 (29.5)	52 (39.7)

[1] Preferred terms; multiple responses possible.

Table 3 Adverse events, serious adverse events and treatment discontinuations in patients without and with cirrhosis, n (%).

Table 4 Treatment discontinuation in treatment-naïve and treatment-experienced patients, n (%).

	BOC-treated		TVR-treated		overall (n = 1,087)
	treatment-naïve (n = 140)	treatment-experienced (n = 147)	treatment-naïve (n = 273)	treatment-experienced (n = 527)	
discontinued treatment	31 (22.1)	42 (28.6)	70 (25.6)	163 (30.9)	306 (28.2)
reason for discontinuation[1]					
lack of response	9 (6.4)	27 (18.4)	21 (7.7)	104 (19.7)	161 (14.8)
adverse events	5 (3.6)	10 (6.8)	21 (7.7)	33 (6.3)	69 (6.3)
lack of compliance	3 (2.1)	1 (0.7)	6 (2.2)	2 (0.4)	12 (1.1)
patient request	10 (7.1)	3 (2.0)	17 (6.2)	22 (4.2)	52 (4.8)
lost to follow-up	5 (3.6)	0	11 (4.0)	4 (0.8)	20 (1.8)
death	2 (1.4)	0	0	1 (0.2)	3 (0.3)
other	4 (2.9)	3 (2.0)	5 (1.8)	9 (1.7)	21 (1.9)

[1] Multiple responses possible.

(including the initial 4 week PEG-IFN + RBV phase) varies between 28 and 52 weeks depending on prior treatment history and response under therapy, presence of cirrhosis, and on-treatment virological response assessed at week 8 and week 24 [19]. Treatment has to be discontinued in patients with HCV RNA ≥ 1000 IU/mL at treatment week 8, ≥ 100 IU/mL at week 12, or confirmed, detectable HCV-RNA at TW 24 according to the established stopping rules.

Fig. 4 shows physician's adherence to the RGT algorithm and stopping rules as specified in the BOC Summary of Product Characteristics, and resultant SVR rates.

Overall, RGT was managed appropriately in around 70 % of patients (treatment duration guided by eRVR, appropriate use of stopping/futility rules, reasonable decision where eRVR data are unavailable); 62.9 % of patients underwent recommended HCV RNA testing at treatment week 8 and 75 % underwent testing at week 12. HCV RNA testing at both week 8 and week 24 was performed in 76 patients (54.3 %); 50 (65.8 %) achieved eRVR. Of patients with an eRVR, the majority were treated in line with recommendations (24 weeks treatment), but 14 patients were subsequently treated for longer than recommended with no additional benefit in terms of SVR compared with those treated for the recommended duration. There was no eRVR determination in 60 patients; 26 of these patients were inappropriately treated for shorter treatment duration, achieving lower SVR rates than similar patients treated for > 44 weeks. Overall, therefore, physicians abbreviated therapy inappropriately or violated the futility rules in around 18.6 % of patients, and in 10 % therapy was unnecessarily extended, leading to increases in cost and potentially adverse events.

TVR-treated patients: Reflecting treatment guidelines, the analysis was restricted to 273 treatment-naïve and 274 prior relapse patients.

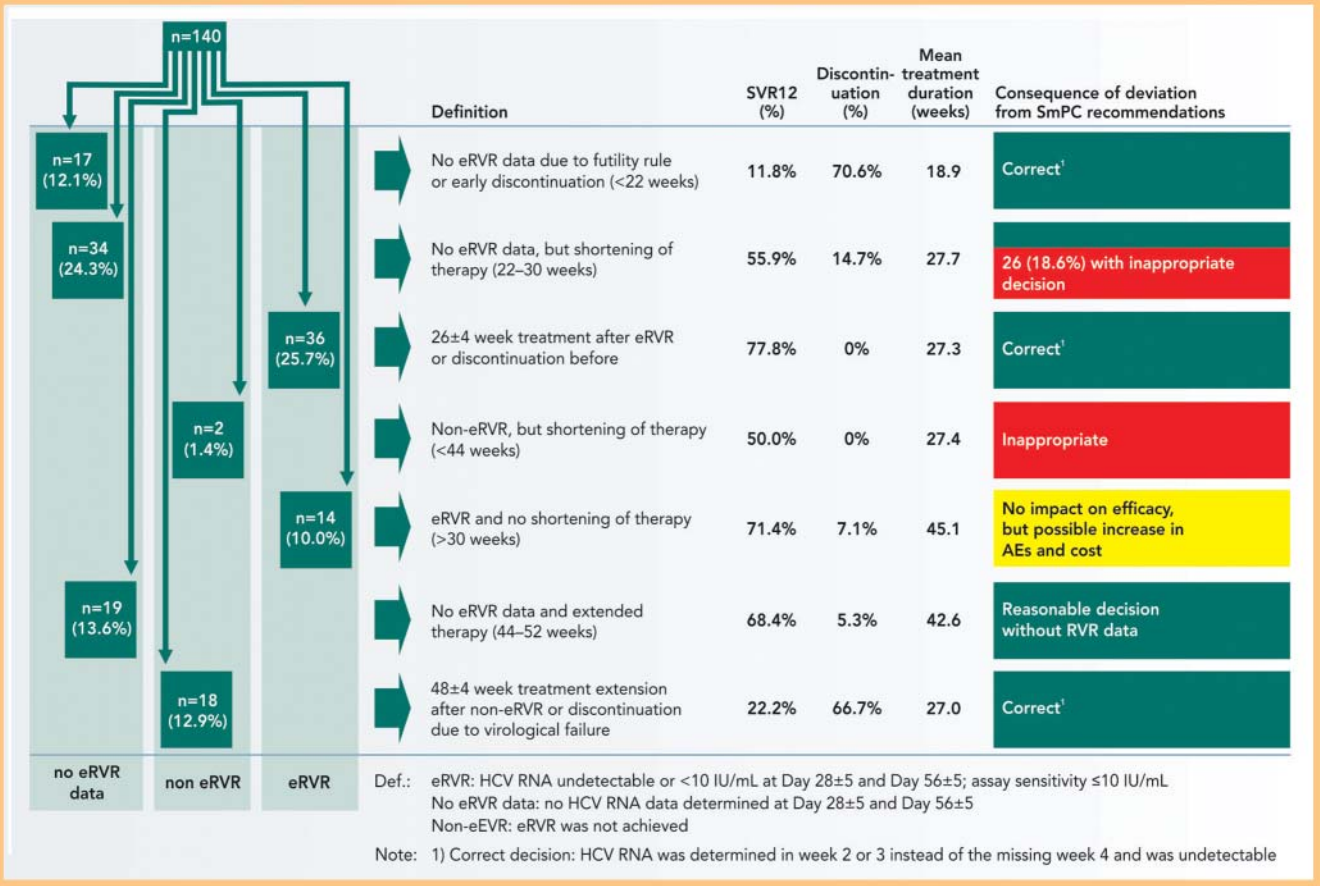

Fig. 4 Adherence to recommended response guided therapy and futility rules versus SVR12 with boceprevir (AEs, adverse events; eRVR, extended rapid virological response; SmPC summary of product characteristics).

The recommended treatment duration for TVR-based triple therapy varies between 24 and 48 weeks depending on prior treatment history, presence of cirrhosis, and on-treatment virological response assessed at week 4 and week 12 [20]. According to stopping rules treatment has to be discontinued in patients with HCV RNA > 1000 IU/mL at treatment week 4 or week 12.

Fig. 5 shows physician adherence to recommended on-treatment testing, RGT and stopping rules, and impact on outcome. Overall, RGT was managed appropriately in approximately 70 % of patients (treatment duration guided by eRVR, appropriate use of stopping/futility rules, reasonable decision where eRVR data are unavailable). eRVR response was assessed in 355 patients (64.9 %); of these 244 (68.7 %) achieved an eRVR. Of those patients with eRVR, the majority subsequently received 24 weeks of treatment in accordance with recommendations and 82.9 % achieved an SVR. However, 63 (25.8 % of patients with an eRVR; 11.5 % of the total population) were subsequently treated for longer than 28 weeks, with no additional benefit in terms of SVR compared with eRVR patients treated for the recommended duration. In addition, 39 patients without eRVR data were inappropriately treated for shorter treatment duration. Overall, therefore, physicians abbreviated therapy inappropriately or violated the futility rules in 7 % of patients, and in 12 % therapy was unnecessarily extended.

Predictors of response

In univariate analysis, SVR was significantly associated with age ≤ 50 years (best cut; p = 0.009), absence of diabetes mellitus (p = 0.001) and being treatment-naive or prior relapser (p = 0.005), absence of cirrhosis, FIB-4 < 3.25, alanine aminotransferase (ALT) ≤ upper limit of normal (ULN), gamma glutamyl transferase (GGT) ≤ ULN, platelets ≥ 150×10^9/L, baseline HCV RNA ≤ 800,000 IU/mL (best cut) (p = 0.0001 for all). Gender, HCV subtype, body mass index, lipid levels (triglycerides, total cholesterol, low density lipoprotein), and IL28B genotype and subtype were not significantly associated with response. When significant factors were carried through to multivariate analysis, only FIB-4 (odds ratio [OR] 0.302; p = 0.0001), GGT ≤ ULN (OR 0.629; p = 0.0001), baseline HCV RNA ≤ 800 000 IU/mL (OR 0.619; p = 0.001) and previous treatment experience (any prior response type; OR 1.407; p = 0.0001) remained significant.

Discussion

In this large cohort of patients treated in routine clinical practice, treatment with BOC- or TVR-based triple therapy achieved overall SVR rates which were about 10 % lower for treatment-naïve patients than those reported in pivotal clinical trials and similar to those in clinical trials for treatment-experienced patients.

In the current analysis, BOC-based triple therapy achieved an SVR rate of 55 % in treatment-naïve patients, compared with 67 % in patients from the SPRINT-2 study [6]. Similarly, 63 % of treatment-naïve patients treated with TVR-based triple therapy achieved SVR, compared with 75 % in the ADVANCE study [5]. In treatment-experienced patients with defined prior treatment

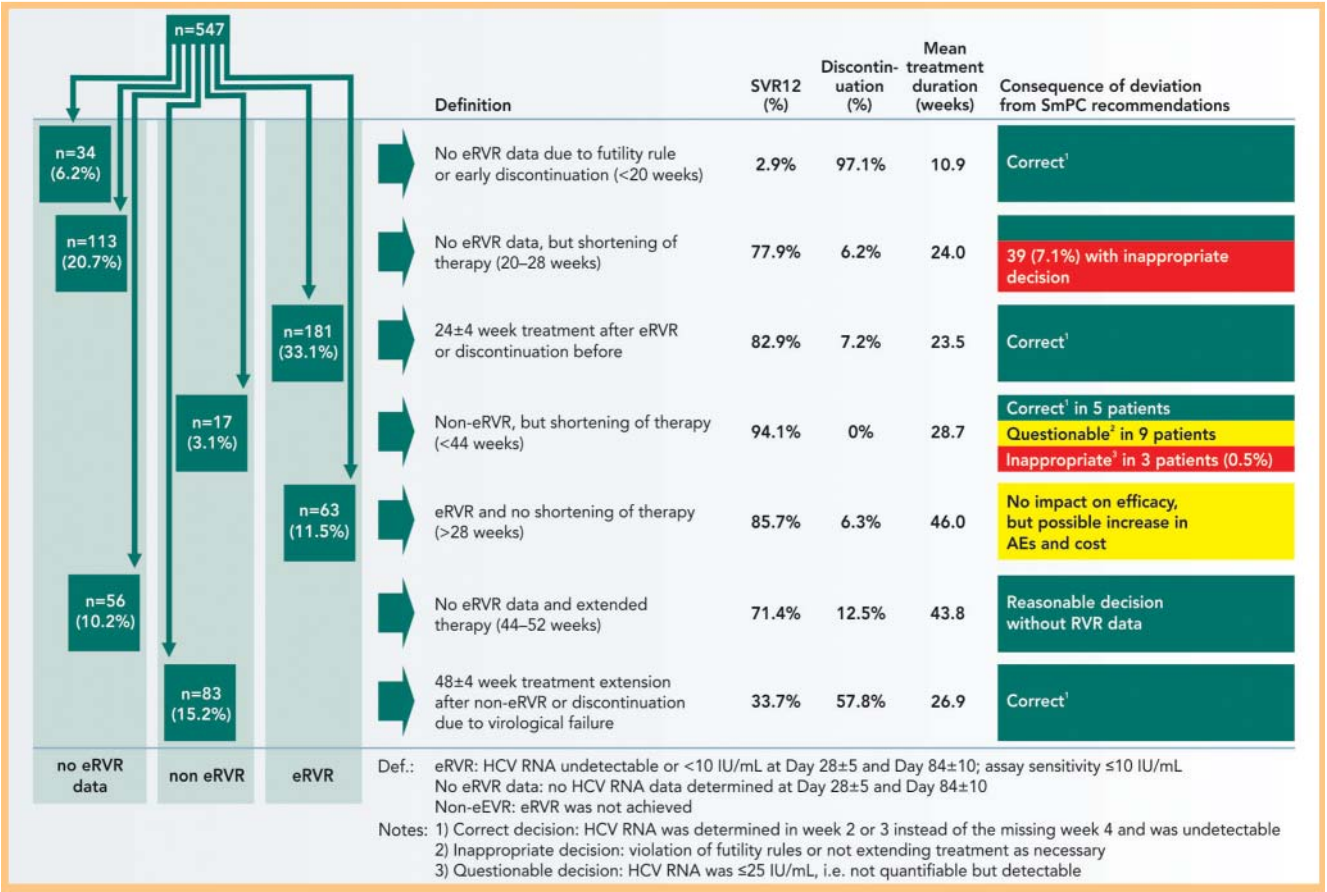

Fig. 5 Adherence to recommended response guided therapy and futility rules versus SVR12 with telaprevir (AEs, adverse events; eRVR, extended rapid virological response; SmPC summary of product characteristics).

histories, BOC-based triple therapy achieved SVR rates of 51 % overall in the PAN cohort (63 % in patients with prior relapse, 35 % in partial responders and 14 % in null responders), similar to that in the RGT arm of the RESPOND-2 study (59 % overall, 69 % in prior relapsers and 40 % in partial non-responders) [7]. TVR-based triple therapy in PAN achieved an overall SVR rate of 58 % in treatment-experienced patients (75 %, 57 % and 25 % in patients with prior relapse, prior partial response and null response, respectively) which were comparable to those achieved in the REALIZE trial (64 % overall; 83 %, 59 %, and 29 %, respectively) [8]. Reflecting the 'real-world' setting of the PAN cohort, detailed prior treatment histories were unavailable for around a third of BOC-treated and almost half of TVR-treated patients. Patient numbers for specified prior response groups were therefore limited in some subgroups, which may have impacted on results. Currently there are limited efficacy data from other large 'real-life' cohorts of patients treated with BOC or TVR. In the US HCV-TARGET observational study, SVR was achieved by 44 % of BOC-treated and 54 % of TVR-treated patients [21]. Similar rates of SVR have been reported in a study of patients treated in a large US integrated care setting [22]. Patients with cirrhosis in the PAN cohort responded less well to triple therapy than those without, but nevertheless SVR rates of up to 40 % were achieved in both treatment-naïve and treatment-experienced patients. This is comparable to other recently published 'real-life' data. For example, an SVR of 43 % was reported in patients with cirrhosis in the US HCV-TARGET study [22] and 42 % was reported in a European cohort of mainly F3 / F4 patients [23]. In general, the pivotal trials of BOC and TVR in treatment-naïve patients included only small numbers of cirrhotic patients and while patients with advanced fibrosis/cirrhosis were reported to show lower rates of SVR, specific figures were not given. However, treatment-experienced cirrhotic patients achieved an SVR rate of 44 % with BOC-based therapy in the RGT arm of RESPOND-2 and 29 % with TVR-based therapy in REALIZE. Higher rates of SVR have been reported for treatment-naïve and treatment-experienced patients with cirrhosis enrolled in the TVR early access programme HEP3002, ranging from 68 % in treatment-naïve patients, to 72 % in prior relapsers and 34 % in null responders [24]. Among treatment-experienced cirrhotic patients in the French Early Access Programme (CUPIC) 74.2 % of relapsers, 40.0 % of partial responders, and 19.4 % of null responders given telaprevir achieved SVR12. Among those given boceprevir, 53.9 % of relapsers, 38.3 % of partial responders, and none of the null responders achieved SVR12 [9].

The safety profile of both BOC- and TVR-based triple therapy in the PAN study was comparable to that reported in clinical trials. The types of adverse events reported were similar, although the rates of common adverse events were generally lower in patients in PAN. This may be a reflection of closer monitoring and reporting in clinical trials compared with routine clinical practice. The overall rate of SAEs in the PAN cohort was similar to that reported in clinical trials. In the current study, patients with cirrhosis experienced around twice the incidence of SAEs compared with those without cirrhosis. However, rates of SAEs in cirrhotic patients in PAN were markedly lower than in the CUPIC cohort [9].

The CUPIC analysis reported a high incidence of SAEs, severe complications (infections, hepatic decompensation) and deaths in treatment-experienced cirrhotic patients managed in routine practice [9]. As the initial reports from the CUPIC cohort were presented soon after the PAN cohort was initiated, it is possible that awareness of these data may have influenced patient selection, or may have led to an intensified monitoring of patients with liver cirrhosis. This may have contributed to lower rates of SAEs seen in cirrhotic patients in the PAN cohort. In line with previously published data in a smaller cohort of patients included in the PAN cohort [25], a decline in renal function (eGFR < 60 mL/min) was reported in about 7 % of patients at week 12 of treatment, which was largely reversed by the end of treatment. Renal impairment was not reported as a safety signal in clinical trials with TVR or BOC, possibly reflecting the selected patient population. Real-world cohorts, such as the PAN cohort, are likely to include a greater proportion of patients with co-morbidities or co-medications which may predispose them to renal dysfunction with BOC and TVR. Although patients with a decline in eGFR were seen in both treatment groups, a higher proportion was observed in patients treated with TVR. A recent retrospective analysis of patients who were treated with triple therapy found that TVR induced a significant variation in eGFR, with a maximal reduction at week 8 of treatment, followed by a return to baseline at week 16 [26]. The authors suggest that this may be a reflection of the inhibition of the drug transporter OCT2 which interacts with creatinine transport, and may therefore be a benign phenomenon. However, follow-up of renal function using eGFR may be advisable during triple therapy, particularly in patients with reduced baseline eGFR. As anemia was found to be more pronounced in patients with decreased renal function, possibly related to accumulation of RBV, substantial RBV dose reductions may be required if eGFR falls on treatment [25].

Although the rates of anemia reported as an adverse event in the current study were lower than those reported in clinical trials, the proportion of patients with anemia on laboratory testing (i. e. hemoglobin < 10 g/dL) was similar, implying under-reporting of anemia by physicians in PAN [5, 6]. Anemia, particularly hemoglobin < 8.5 g/dL, was more commonly reported in cirrhotic compared with non-cirrhotic patients included in PAN, however the incidence was lower than in CUPIC [9]. Dose reduction of RBV was markedly more common in cirrhotic patients in the PAN cohort (48.6 % of BOC-treated patients and 30.8 % of TVR-treated patients) compared with the CUPIC cohort (14.6 % and 17.1 %, respectively) [9], but was similar to that reported more recently in patients with advanced cirrhosis treated with TVR in the early access programme (40 %) [27]. Details on the use of erythropoietin for anemia management were not specifically collected in PAN, as erythropoietin is not approved in Germany for the use in this indication. In general, early RBV dose reduction is the preferred strategy for anemia management according to prescribing information for both BOC and TVR, and has been shown not to affect the rate of SVR following triple therapy [28].

Overall, the majority of patients in the PAN cohort were managed according to recommended treatment schedules. However, in a significant proportion futility rules were violated and patients underwent unnecessarily extended treatment duration. A small number of patients were treated for a shorter period than required. Similar findings were reported in the HCV-TARGET cohort, where RGT rules were appropriately applied in the majority of patients, but futility rules were ignored in 20 % of BOC-treated patients with HCV RNA > 100 IU/mL at week 12 and 16 % of TVR-treated patients with HCV RNA > 1000 IU/mL at week 4 [29]. Given the potential impact of inappropriate treatment on response, incidence of adverse events and treatment costs, and the possible development of resistant variants, it is important that physicians in routine practice are encouraged to follow RGT algorithms and apply stopping/futility rules appropriately.

Predictors of response in the PAN cohort (degree of fibrosis, baseline HCV RNA, treatment history) were similar to those previously reported. In the current analysis, the strongest independent predictor of response was a FIB-4 score of less than 3.25, which has been shown to be a surrogate for advanced fibrosis (METAVIR F3 – F4) [30]. Although IL28B genotype was not a strong predictor of response in our study, IL28B genotype data were only available for a small subset of patients, limiting the strength of our analysis for this variable.

The main limitations of the current analysis are those generally associated with observational studies. However the current study provides valuable 'real-life' data in patients treated with BOC- and TVR-based triple therapy. Despite the development of new generations of DAAs, the high costs will limit access severely in most regions of the world, and triple therapy may remain or become a primary treatment option for many patients with HCV genotype 1 infection depending on pricing and local policies.

In conclusion, the efficacy and safety of BOC- and TVR-based triple therapy in treatment-naïve and treatment-experienced patients included in the large, 'real-world' PAN cohort were largely comparable to that reported in pivotal clinical trials, although SVR rates were lower overall. The majority of patients were managed appropriately using recommended response-guided treatment algorithms. However, futility or treatment extension rules were violated in a significant proportion of patients, with potential impacts on response, incidence of adverse events and treatment costs.

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