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Effect of Peginterferon or Ribavirin Dosing on Efficacy of Therapy With Telaprevir in Treatment-Experienced Patients With Chronic Hepatitis C and Advanced Liver Fibrosis

A Multicenter Cohort Study

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Abstract: We investigated the safety, efficacy, and impact of ribavirin and peginterferon dose reduction on complete early virologic response and sustained virologic response (SVR) to triple therapy with telaprevir in treatment-experienced patients with advanced liver fibrosis.

Treatment was initiated for 211 patients who failed treatment with peginterferon and ribavirin, with bridging fibrosis (F3, n = 68) or cirrhosis (F4, n = 143), including 103 (49%) null-responders (NR), 30 (14%) partial responders (PR), and 78 (37%) relapsers (REL). Impaired liver function (ILF) platelets $<100{,}000/mm^3$ or albumin <35 g/L were present in 40 patients. The distribution of hepatitis C virus subtypes was: 1a, 1b, or 1, with undetermined subtype for 10 (5%), 187 (89%), and 14 (6%) patients, respectively. Treatment was started with peginterferon alpha-2a or alpha-2b, ribavirin, and telaprevir at standard doses.

The overall SVR24 rate was 56% and was lower in cirrhotic patients (NR: 35%, PR: 40%, and REL: 63%, respectively) than in patients with bridging fibrosis (NR: 50%, PR: 75%, and REL: 75%, respectively). The lowest probability of SVR24 was in NRs with ILF (26%). The SVR24 rate significantly decreased in NRs receiving <60% vs >60% of the total ribavirin dose (23% vs 44%, respectively) or <80% vs >80% of the total ribavirin dose (33% vs 48%, respectively). A significant SVR24 decrease was noted subsequent to a total peginterferon dose reduction, both when comparing patients who received <60% vs >60% of the total dose (NR: 0% vs 44%; REL: 33% vs 68%) and patients who received <80% vs >80% of the total dose (NR: 17% vs 50%; REL: 46% vs 71%).

Serious adverse events were observed in 31 patients (15%). Deaths occurred in 4 patients. All of the deceased subjects were cirrhotic members of the ILF (baseline serum albumin level <35 g/L and/or platelet count $<100{,}000/mm^3$) group.

Ribavirin dose reduction did not affect efficacy in REL but did in NR. Peginterferon dose reduction decreased the SVR24 rate for all groups, particularly in prior NR. ILF increased the risk of fatal complications with a low probability to achieve SVR24. One solution might be to provide wide and early access to novel, efficient, and safe interferon-free combinations to treatment-experienced patients, particularly those with liver cirrhosis.

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Abbreviations: BOC = boceprevir, cEVR = complete early virologic response, DAA = direct-acting antiviral, ETR = end-of-treatment response, Hb = hemoglobin, HBV = hepatitis B virus, HCV = hepatitis C virus, HCVRNA = hepatitis C virus ribonucleic acid, HIV = human immunodeficiency virus, LLOQ = lower limit of quantification, NR = null-responder, PegIFN = pegylated interferon, PI = protease inhibitor, PR = partial responder, RBV = ribavirin, REL = relapsers, RVR = rapid virologic response, SAE = serious adverse event, SCAR = severe cutaneous adverse reaction, SVR = sustained virologic response, SVR24 = sustained virologic response at 24 weeks posttreatment, TVR = Telaprevir.

INTRODUCTION

Approval of the first 2 direct-acting antiviral drugs (DAAs), telaprevir (TVR) and boceprevir (BOC), was a milestone in

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the development of antiviral treatments for chronic hepatitis C. The addition of either TVR or BOC to the existing regimen (peginterferon-alpha + ribavirin [RBV]) significantly increased the probability of achieving a sustained virologic response (SVR), even in the most difficult-to-treat patients.[1–5]

Triple therapy with TVR results in a higher proportion of patients achieving SVR but also in more drug-related adverse events (AEs), such as anemia, neutropenia, or skin reactions.[1–5] Data from phase III studies of TVR are limited for patients with advanced liver fibrosis or cirrhosis because only a small subset of these populations has been enrolled in trials, and there are no strict criteria for patient selection. Groups selected for phase III trials do not reflect the population of patients treated in a real-life setting.

Real-world studies, such as CUPIC[4,5] or other cohorts,[6–8] have assessed the efficacy and safety of triple therapy with first-generation protease inhibitors (PIs), but the number of prior null-responders (NRs) in the analyzed cohorts is still relatively low.[2–5] The cohort study on the largest group containing NRs of 436 patients with advanced fibrosis (HEP3002) is ongoing,[9] and data collected after 16 weeks of treatment have been published.

The aim of our study is to evaluate the efficacy and safety of TVR-containing therapy in patients with advanced liver fibrosis, mainly in the most difficult-to-treat patients—prior NRs—and to assess the influence of RBV or pegylated interferon (PegIFN)-alpha dose reduction on treatment efficacy.

PATIENTS AND METHODS

AdvEx (Advanced and Experienced), a multicenter cohort study, was conducted in 16 Polish sites in real-life settings. We analyzed medical charts containing clinical and laboratory data from 211 patients who received triple therapy from September 2011 to May 2012. Treatment-experienced patients infected with genotype 1 hepatitis C virus (HCV) with bridging fibrosis (F3) or compensated cirrhosis (Child-Pugh class A) received triple therapy with TVR, PegIFN-alpha, and RBV. The fibrosis stage was assessed by liver biopsy in 121 patients or the non-invasive tests: FibroScan (Echosens, Paris, France) in 80 patients or Fibrotest (BioPredictive, Paris, France) in 10 subjects.

Liver biopsies were performed using a Hepafix needle (Braun Melsungen AG, Melsungen, Germany). The degree of fibrosis was classified according to METAVIR scoring system (F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with few septa, F3 = numerous septa without cirrhosis, and F4 = cirrhosis). FibroScan cut-off to diagnose bridging fibrosis and cirrhosis was 9.5 and 12.5 kPa, respectively.[10] Fibrotest values used for diagnosis of F3 and F4 were 0.59 and 0.75, respectively, per manufacturer's recommendations.

Patients for whom interferon-based treatment was contraindicated or who were co-infected with HBV and/or HIV were excluded. Patients with a history of receiving DAAs were not eligible. The main goal of the study was to evaluate the efficacy and safety of triple therapy in this difficult-to-treat patient population. The secondary goals were to assess the effect of RBV or PegIFN-alpha dose reduction on the SVR measured at 24 weeks posttreatment (SVR24) and the influence of a hemoglobin level decrease on treatment efficacy.

Patients were treated with TVR at a dose of 750 mg every 8 hours in combination with PegIFN-alpha and RBV for the initial 12 weeks. Previous relapsers with bridging fibrosis who achieved undetectable HCV RNA at weeks 4 and 12 continued treatment with PegIFN-alpha and RBV for an additional 12 weeks (total treatment duration, 24 weeks). All patients with liver cirrhosis, regardless of their response to previous PegIFN-alpha + RBV treatment, and prior partial responders (PRs) or NRs with F3, were treated with PegIFN-alpha and RBV for a subsequent 36 weeks (Fig. 1).

Particular types of PegIFN-alpha (Pegasys or PegIntron) and RBV (Copegus or Rebetol) were prescribed at the discretion of the attending physician. The initial doses of PegIFN and RBV were prescribed according to manufacturer's recommendations. Treatment efficacy was determined by measuring HCV RNA levels at baseline, treatment weeks 4, 12, 24, and 48, and 24 weeks after treatment completion using polymerase chain reaction. Two assays were used to measure HCV RNA, depending on local practices at the testing site: Roche COBAS TaqMan with a lower limit of quantification (LLOQ) of 25 IU/mL or Abbott RealTime with an LLOQ of 12 IU/mL. Standard definitions for rapid virologic response (RVR), complete virologic response (cEVR), and sustained virologic response (SVR24) were applied. Therapy was stopped for patients with a HCV RNA > 1000 IU/mL at week 4 or 12 or at a detectable level at week 24 or thereafter.

Efficacy analyses were performed on an intent-to-treat basis. The number of patients achieving a virologic response was calculated for the overall population and for subgroups according to their prior treatment response. All AEs and serious adverse events (SAEs) were recorded, with special attention paid to hematologic abnormalities leading to the discontinuation of 1 or more drugs or to a reduction of the PegIFN-alpha/RBV dose. Safety measurements were performed at baseline; at weeks 2, 4, 6, 8, and 12; and then monthly until the end of therapy. Additional visits were performed if clinically necessary.

Interventions to counteract anemia included RBV dose reduction and/or blood transfusion. Reduction of the TVR dose as well as its resumption after discontinuation was prohibited. Erythropoietin administration is not permitted in Poland. (It is approved only for hemodialysis or for treatment of anemia induced by chemotherapy for neoplastic diseases.) PegIFN-alpha reductions due to neutropenia and/or thrombocytopenia were recommended in accord with product characteristics. Ethical approval was not necessary for this observational study, conducted in real-life setting with approved drugs.

Statistical Analysis

Data are presented as absolute numbers. No sample size was planned. All patients who started the treatment are included in the analysis, and efficacy analyses were performed on an intent-to-treat basis. Missing virological measurements were imputed as treatment failures.

Comparisons among independent groups were completed with the Mann–Whitney *U* test or Fisher's exact test and within-group comparisons were made using Chi-squared tests.

Multivariate linear regression models were used to identify predictors of treatment failure.

Statistical analyses were performed with Statistica 8.0 (Statsoft, Tulsa, OK).

RESULTS

Patient Characteristics

Two hundred eleven Caucasian subjects ages 20 to 75 (mean age 54.5 years), 131 men and 80 women, were enrolled in the study. The prior treatment response was relapse (REL) for 78 patients (37%), a partial response (PR) for 30 patients (14%),

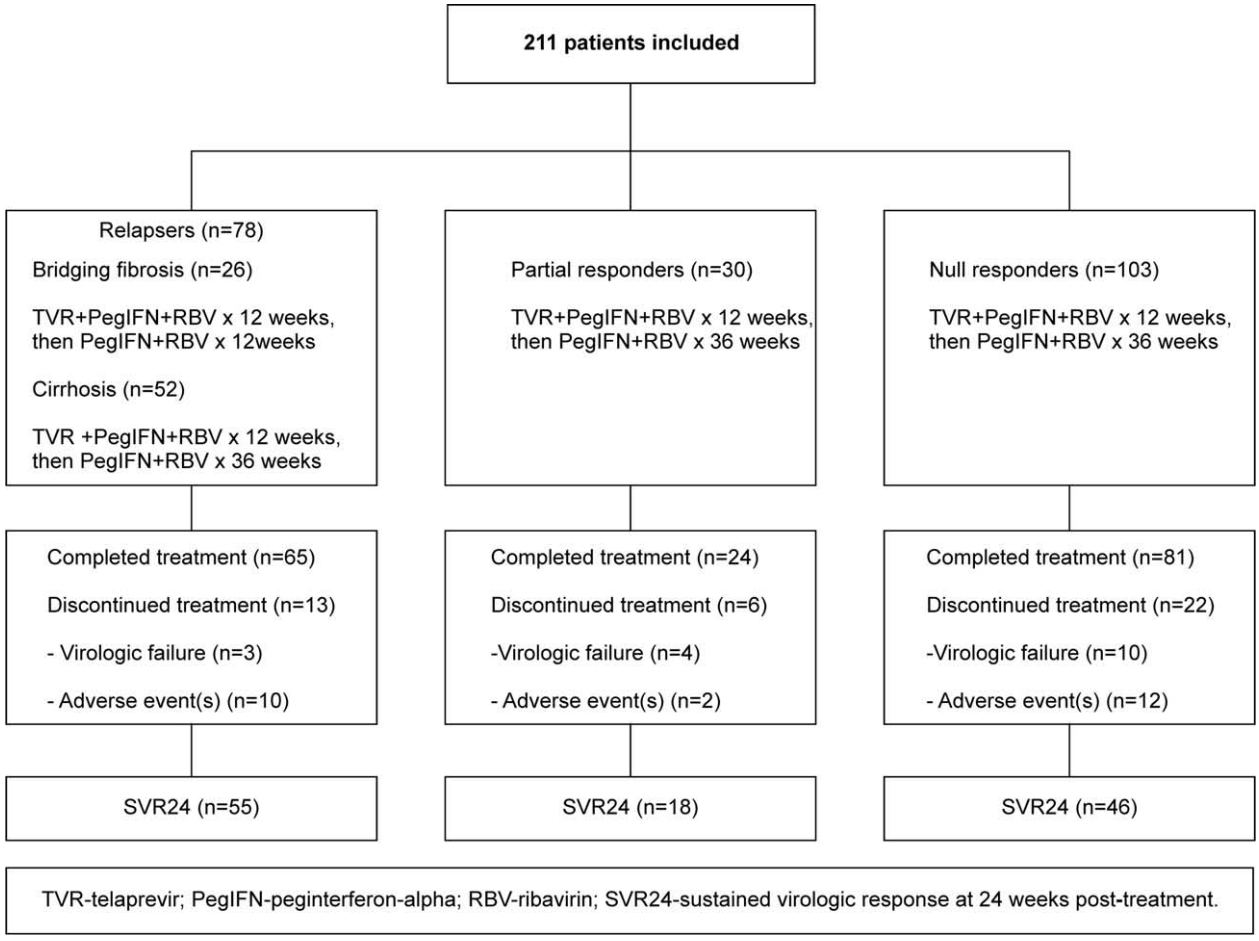

FIGURE 1. Flow chart of study population.

or a null-response (NR) for 103 subjects (49%). The distribution of HCV subtypes was: 1a, 1b, or undetermined in 10 (5%), 187 (89%), and 14 (6%) patients, respectively.

The majority of patients (143; 68%) were cirrhotic, while bridging fibrosis (F3) was diagnosed in 68 (32%) patients. Before treatment, all patients met the criteria of category A according to Child-Pugh score, but 40 (19%) patients had laboratory results indicating impaired liver function (ILF)[9] (serum albumin level <35 g/L and/or a platelet count $<100{,}000/mm^3$); based on observations of the CUPIC (Compassionate Use of Protease Inhibitors in Cirrhotics) cohort, these patients were thus at risk for the occurrence of severe or fatal complications.[2,3] One hundred sixty-one patients (76%) were treated with PegIFN-alpha2a, and 50 patients (24%) received PegIFN-alpha2b. The characteristics of the patients are listed in Table 1.

Treatment Efficacy and Its Relationship With PegIFN and RBV Dose Reduction

The key virologic endpoints are shown in Figure 2. Overall, 61% of patients achieved undetectable HCV RNA at week 4 (defined as a RVR). The highest rate of RVR was observed in prior relapsers (74%); lower rates were noted in PRs (56%) and NRs (48%). The percentage of patients who had undetectable HCV RNA at week 12 were 92%, 96%, and 75% for relapsers, PRs, and NRs, respectively. The overall cEVR rate was 83%.

During the initial triple therapy period (the first 12 weeks), the RBV dose was reduced due to significant anemia (<10.0 g/dL) in 107 (50%) patients, and blood transfusion combined with RBV dose reduction occurred in 22 patients (10%) without a significant difference in the overall cEVR rate (79% vs 83%, $P = 0.31$, not clinically significant—NCS). Generally, RBV dose reduction was administered according to the manufacturer's recommendations, but in some cases of severe anemia, RBV doses were reduced by the treating physicians even to 400 mg or 200 mg/day.

There were no statistically significant differences between cEVR rates in patients who received a full RBV dose (overall: 88%; REL: 94%, PR: 79%, and NR: 84%) or who needed RBV dose reduction (overall: 82%; REL: 93%, PR: 92%, and NR: 74%). Even patients who received the lowest RBV doses of 200 to 400 mg were able to achieve cEVR at a rate of 75% to 83%, which was similar to that for patients receiving higher doses. However, none of the 7 subjects who discontinued RBV and TVR achieved cEVR. Patients who received $<60\%$ of the expected total RBV dose for 12 weeks of treatment demonstrated a significantly lower probability of achieving cEVR (53% vs 87% in patients who received $>60\%$ of the expected dose, $P = 0.04$). The rate of cEVR was significantly lower if the RBV dose reduction was applied within the initial 4 weeks (59%) compared with a dose reduction applied between weeks 4 and 12 (83%, $P = 0.03$); this difference was particularly notable

TABLE 1. Baseline Characteristics of the Patients

	Relapsers	Partial Responders	Null Responders	Overall
Enrolled patients	78 (37%)	30 (14%)	103 (49%)	211
Females	26 (12%)	13 (6%)	41 (20%)	80 (38%)
Males	52 (25%)	17 (8%)	62 (29%)	131 (62%)
Mean age (range), yr	51.4 (24–75)	55.3 (31–69)	56.7 (20–72)	54.5 (20–75)
Fibrosis stage F3	26 (12%)	10 (5%)	32 (15%)	68 (32%)
Liver cirrhosis	52 (25%)	20 (9%)	71 (34%)	143 (68%)
Impaired liver function	14 (7%)	3 (1%)	23 (11%)	40 (19%)
Treated with PegIFN-alpha2a	60 (28%)	25 (12%)	76 (36%)	161 (76%)
Treated with PegIFN-alpha2b	18 (9%)	5 (2%)	27 (13%)	50 (24%)

among NRs (44% vs 75%, respectively, $P = 0.04$). Patients with an on-treatment Hb level below 12 g/dL achieved a significantly higher cEVR rate than those with Hb > 12 g/dL (85% vs 66%, respectively, $P = 0.019$).

The end-of-treatment response (ETR) and SVR24 rates were lower than the cEVR rates for all groups of patients (Fig. 2). The overall SVR24 rate was 56% (REL: 71%, PR: 60%, and NR: 45%). The SVR rate was even lower in patients with ILF (33%), especially among NRs (26%).

The proportion of SVR24 was lowest in patients who received <60% of the total recommended RBV dose and highest in subjects who received more than 80% ($P = 0.04$). The exception was the group of PRs who showed the highest SVR24 rate among patients who received <60% of the total recommended RBV dose, but reliability of data for this group was affected by its small size (Fig. 3).

The SVR rate significantly ($P < 0.003$) decreased in NRs who received <60% as compared with >60% of total planned RBV dose (23% vs 44%, respectively) or received <80% in comparison with >80% of the planned dose (33% vs 48%, respectively). A RBV dose reduction to <600 mg/day significantly decreased the SVR24 rate in NRs (32% vs 47% in NR who received >600 mg/day; $P = 0.001$) and insignificantly in relapsers (77% vs 66% in REL who received >600 mg/day). A decrease in the hemoglobin level <10 g/dL improved the SVR rate in relapsers (81% vs 64% in REL with Hb level >10 g/dL; $P = 0.005$) but worsened it in NRs (37% vs 51% in NR with Hb level >10 g/dL; $P < 0.001$).

As shown in Figure 4, reduction of the total PegIFN dose is probably more important than dose of RBV for SVR prediction. A significant SVR24 decrease was caused by total peginterferon dose reduction when comparing patients receiving, respectively, <60% and >60% of the planned dose (NR: 0% vs 44%, $P < 0.001$; REL: 33% vs 68%, $P = 0.03$) and patients receiving, respectively, <80% vs >80% of the planned total dose (NR: 17% vs 50%, $P = 0.02$; REL: 46% vs 71%, $P = 0.04$).

Among patients who received <60% of the recommended PegIFN dose, only relapsers achieved an SVR24 rate of 33%. None of the PRs or NRs receiving <60% of the total planned dose achieved SVR24. On the other hand, a peginterferon weekly dose reduction to <75% of initial dose significantly ($P < 0.001$) decreased the SVR24 rate both in NRs (22% vs 54%, respectively) and relapsers (57% vs 73%, respectively) when compared with counterparts who received at least 75% of the recommended dose.

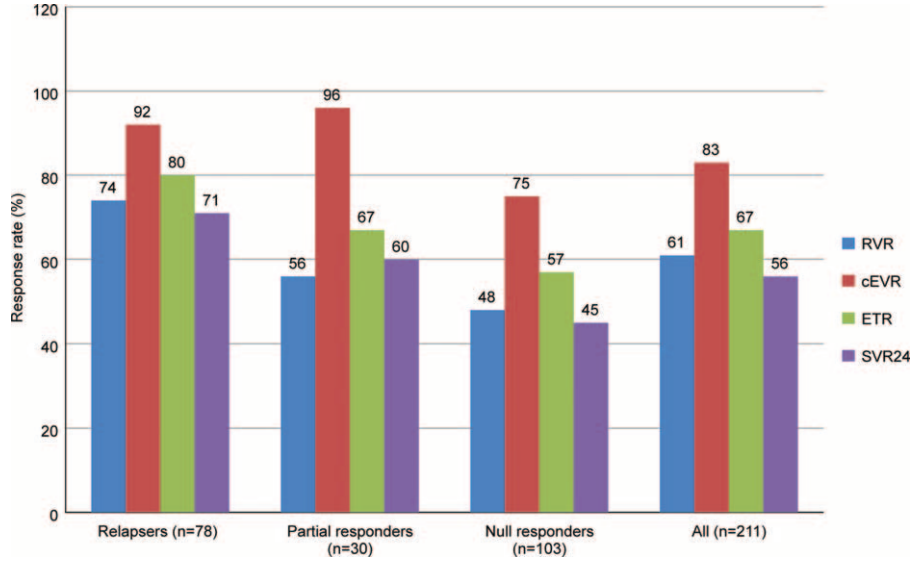

FIGURE 2. Rapid virologic response (RVR), complete early virologic response (cEVR), end-of-treatment response (ETR), and sustained virologic response (SVR24) rates among relapsers, partial responders, and null-responders.

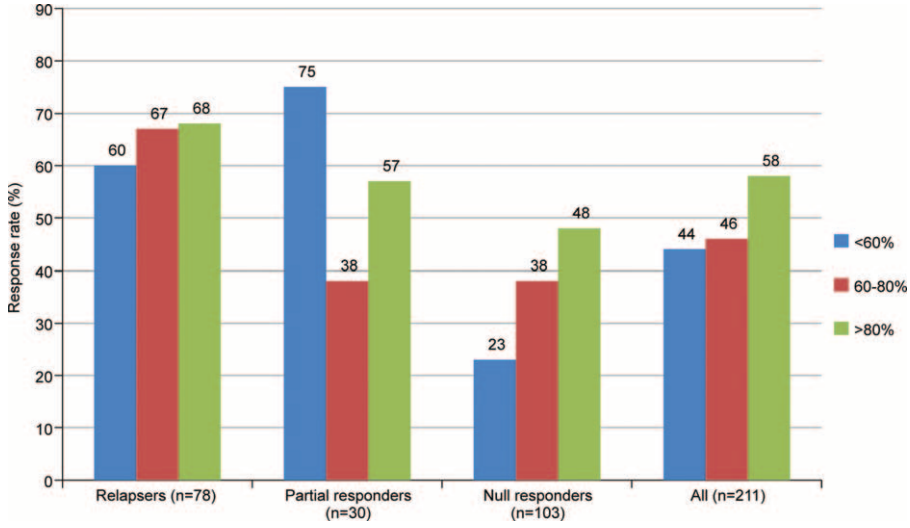

FIGURE 3. Sustained virologic response (SVR24) according to total ribavirin dose received (<60%, 60% to 80%, or >80% of the planned dose).

The SVR24 rate was higher in patients with F3 (67% overall) than in patients with cirrhosis (46% overall). This pattern was observed in all groups (Fig. 5): REL (76% vs 63%), PR (75% vs 40%), and NR (50% vs 35%).

In multivariate analysis (Table 2), 4 independent factors were associated with treatment failure: baseline albumin level <35 g/L, baseline PLT count <100,000/mm^3, prior null response and PegIFN dose reduction. Age, sex, baseline hemoglobin level, and type of IFN used were tested in univariate analysis and were not significant.

Adverse Events

The incidence of AEs during TVR containing triple therapy in our population of patients with advanced fibrosis was higher than in registration studies.[1,2] SAEs were observed in 31 patients (15%). Death occurred in 4 patients (3 men and 1 woman), but only 1 patient with concomitant diabetes mellitus died during the triple therapy regimen (TVR + PegIFN-alpha + RBV) at week 7, due to hypoglycemia. Two deaths occurred during the dual-treatment period, 1 at week 20 (a central nervous system hemorrhage), and the other at week 36 (hepatocellular carcinoma and hepatic decompensation). A fourth death occurred after treatment completion, at week 52, due to sudden cardiac arrest that was not related to the antiviral treatment. The 3 deaths may have been related to the administered drugs, especially interferon. All of the deceased subjects were cirrhotic belonging to group of ILF (baseline serum albumin level <35 g/L and/or platelet count <100,000/mm^3), so they were at risk for the occurrence of death or severe complications.

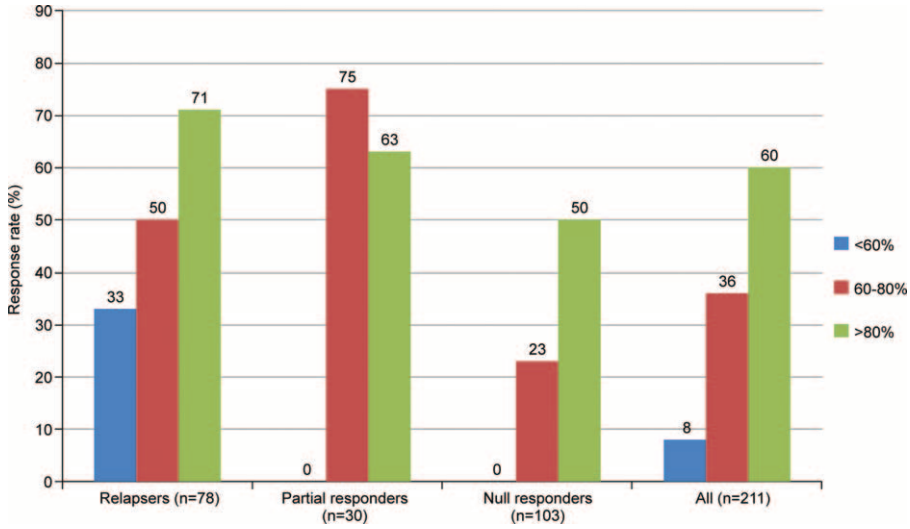

FIGURE 4. Sustained virologic response (SVR24) according to total peginterferon dose received (<60%, 60% to 80%, or >80% of the recommended dose).

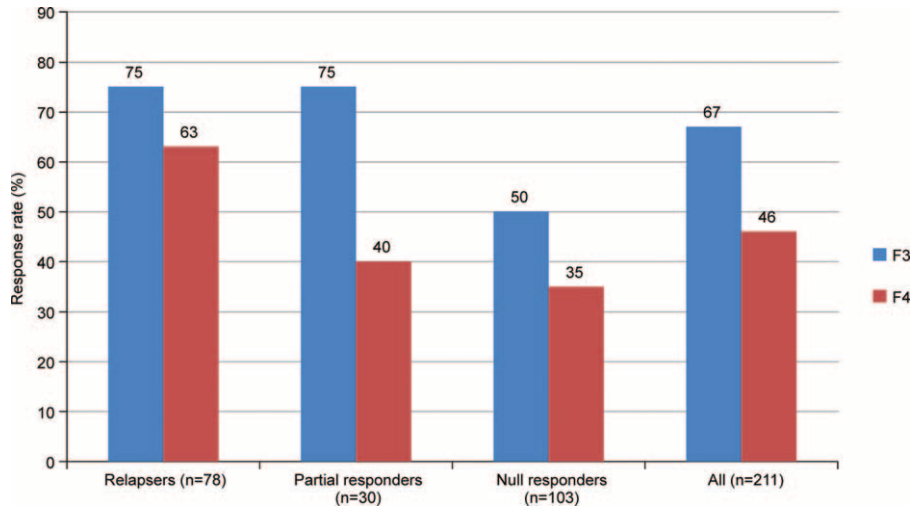

FIGURE 5. Sustained virologic response (SVR24) according to the stage of fibrosis.

Treatment was stopped due to an AE in 17 patients (8%). Anemia with Hb levels below 8.5 g/dL was observed in 41 patients (19%), and Hb levels between 8.5 and 10.0 g/dL were observed in 66 subjects (31%). RBV dose reduction was needed for 107 patients (50%), and blood transfusion was necessary for 22 (10%) patients. Anorectal AEs were reported by 77 (36%) patients. Dermatological side effects were observed in 80 patients (38%); a mild to moderate rash was reported by 72 patients (34%), and a severe rash was reported by 3 (1%) patients. Five cases of severe cutaneous adverse reactions were observed. Cutaneous AEs were the reason for permanent treatment discontinuation for eight (4%) patients.

DISCUSSION

The efficacy of triple therapy with PegIFN, RBV, and TVR significantly increased in comparison to dual therapy, especially in treatment-naïve patients and those who relapsed after previous antiviral treatment.[1,2] Data from clinical trials have shown a lower efficacy in previous PRs and NRs and in patients with advanced fibrosis, but from 2011 to 2013 there was no better therapeutic option for these patients. Patients with advanced fibrosis, particularly cirrhosis,[11,12] were considered to be in urgent need of treatment. Preliminary data from real-life studies such as CUPIC[4,5] revealed the hazards of treatment-related AEs in patients with advanced liver disease, but the expected benefits to the patients seemed to outweigh the potential risks. As confirmed by a growing number of studies,[13–16] the regression of fibrosis and even cirrhosis is possible in patients who achieve SVR. Effective antiviral treatment significantly reduces development of decompensation, hepatocellular carcinoma, and liver-related mortality.[16–20] Unfortunately, in more advanced liver disease, the probability of achieving SVR is lower. The differences between cirrhotic and noncirrhotic patients who were evaluated in the REALIZE trial[2,21] were significant: the SVR24 rate among patients with fibrosis F3 to F4 was 58% versus 75% in subjects with a lower degree of liver injury. In our F3 to F4 group, the overall SVR24 rate was similar (56%), but the rate of SVR among patients with cirrhosis was higher in the AdvEx cohort than in the REALIZE study group (46% vs 34%, respectively). The SVR rate among relapsers with fibrosis F3 to F4 was lower in the AdvEx group (71%) than in the REALIZE group (84%) but was comparable with CUPIC (74.2%) data. A possible reason for this difference is that patients who are enrolled in real-world studies are more difficult to treat, and many of the patients did not meet the eligibility criteria for clinical trials due to advanced liver disease.

TABLE 2. Factors Related to Treatment Failure: Multivariate Analysis

	OR	95% CI	*P* Value
Baseline platelet count $<100{,}000/mm^3$	2.001	1.335–3.233	0.035
Baseline albumin level <35 g/L	0.055	0.014–0.221	<0.001
Ribavirin dose reduction	0.883	0.316–2.471	0.813
PegIFN-alpha dose reduction	0.292	0.088–0.971	0.045
Prior null response	0.234	0.113–0.812	0.015

CI = confidence interval, OR = odds ratio.

Among AdvEx PRs, the SVR rate was 60%, which was higher than in REALIZE F3 to F4 (44%) and CUPIC (40% for cirrhotic patients only). The results obtained for our cohort may be biased due to the relatively small number of patients enrolled (30 vs 135 patients in CUPIC), so the SVR rates achieved by CUPIC patients seem to be closer to clinical reality. The results for a PRs group of 139 patients in the HEP3002 trial[22] were comparable (55%); however, in contrast to AdvEx, inclusion and exclusion criteria of HEP3002 were strict and similar to those used in TVR registration trials.

The group of AdvEx NRs (103 patients) is one of the largest such cohorts among published real-world studies with available SVR24 data. For example, the CUPIC NR cohort treated with TVR consisted of only 31 subjects, and the Hamburg single center cohort[6] had <13 subjects (PRs and NRs were combined). The only published observation of a larger group, the HEP 3002 trial,[22] included 294 previous NRs.

The SVR rate among AdvEx NRs was 48% (50% in patients with bridging fibrosis, 35% in cirrhotic patients). These

results are much better than those achieved in the REALIZE study (28%) or the CUPIC cohort (19.4%), and even better than those obtained in the HEP 3002 trial (overall 34%; 41.2% in patients with F3 and 28.6% in cirrhotic patients). One reason for such a high rate of SVR in the most difficult-to-treat patients could be that treatment was performed in experienced medical centers, the majority of which had conducted phase II or III trials with TVR. The growing knowledge of the first real-world safety data for cirrhotic patients was very important because it revealed potential risk factors and AEs that were not seen in a clinical trial setting. Those experiences allowed better preparation for treatment (eg, close attention to prophylaxis for potential AEs) and closer monitoring focused on symptoms that are consistent with the possible occurrence of an SAE. As a result, patients were treated with as high as possible doses of PegIFN or RBV, and the TVR regimen was not discontinued without significant reason.

The safety profile of therapy was similar to other real-world studies. Anemia requiring an RBV dose reduction occurred in 1/2 of our patients. Sulkowski et al[23] showed that anemia occurring during dual therapy with PegIFN-alpha and RBV does not affect treatment efficacy. However, cases of severe anemia that lead to RBV reduction or treatment discontinuation were observed much less frequently during dual compared with triple therapy.[1,2,4,5] RBV dose reduction, even to a dose below the lowest recommended by the manufacturer, did not affect the cEVR rate of our patients. However, further analysis of the influence of the total RBV dose administered on SVR24 rate showed a difference between patients who received <60% of the total recommended dose of RBV and those who received more than 80%. It seems that in the most difficult-to-treat patients, the antiviral potency of the 3 drugs allows achievement of cEVR regardless of RBV dose reduction, but subsequent treatment with PegIFN-alpha and RBV without DAA drugs requires at least 80% of the total planned dose of RBV.

The virologic response was also much higher in patients who received more than 80% of the total planned PegIFN-alpha dose than for those receiving 60% to 80% or <60%. The probability of achieving SVR24 was low in the relapser group (33%), but an SVR was practically unreachable for PRs or NRs receiving <60% of the planned dose. It seems that in prior NRs, particularly in those with advanced fibrosis, the classic McHutchinson's rule of ''3 × 80%''[24] is still valid for triple treatment with TVR. In PRs and NRs who need reduction of Peg-IFN to <60% of the planned dose, termination of treatment and waiting for IFN-free options should be considered.

SAEs were observed less frequently in our study than in the CUPIC cohort (15% vs 53.8%, respectively), which could be explained by the lower number of patients with ILF in our study (albumin level <35 g/L and/or platelet counts <100,000/mm^3). This group of patients included 40 patients (19%) in AdvEx and 142 patients (28%) in the CUPIC cohort.[5] The incidence of death was also less frequent in the AdvEx cohort compared with the CUPIC cohort (1.7% vs 2.7%, respectively). None of the fatal cases in the AdvEx cohort was assessed as related to TVR, although 3 of the deaths may have been related to PegIFN.

One limitation of our study is the retrospective method of data collection. Treatment was conducted in 16 medical centers without a previously established plan and without a protocol defining uniform procedures (eg, the management of AEs or guidelines for the reduction of medication doses). In general, the recommendations contained on drug labels were respected, but in some cases, the treating physicians decided to reduce RBV doses to 400 mg or even 200 mg/day, believing that it would be better to maintain a minimal dose of RBV than to completely discontinue its administration. Stopping RBV would result in the discontinuation of TVR as well and make therapeutic success practically unachievable. The other limitation of our study was the small size of the PR group, which complicated the statistical analysis.

One strength of our study was the large group of prior NRs with advanced fibrosis, which was unprecedented in previously published real-world studies. We also performed an analysis of the influence of RBV and PegIFN total dose reduction on cEVR and SVR24. Similar analyses have not been published. We have shown that it is possible to obtain a better outcome than in other real-world cohorts,[4–8] provided that full or only slightly reduced doses of PegIFN and/or RBV are used. However, when therapies using a new generation of DAAs have reached efficacy approaching 100%,[25–30] even in treatment-experienced patients, the SVR24 rates achieved by our patients (bridging fibrosis, 50%; cirrhosis, 35%) were unsatisfactory.

Interferon-free, safe combinations of at least 2 DAAs (sofosbuvir + simeprevir, sofosbuvir + daclatasvir, sofosbuvir + ledipasvir, paritaprevir/r + ombitasvir + dasabuvir) with or without RBV seem to be the treatment of choice for patients with advanced liver disease.[3–5,25–32] The risk/benefit ratio strongly favors IFN-free treatment in all chronic hepatitis C patients, particularly in prior NRs with liver cirrhosis. This type of therapy combines high efficacy, favorable safety profile, and a short duration.

Unfortunately, the high costs of such combinations make this type of treatment unavailable in numerous countries presently and in the next few years. Thus, triple therapy with first generation PIs will remain the best option for patients who are suffering from chronic hepatitis C in those countries. Triple treatment of naïve patients or prior relapsers during an early stage of fibrosis seems to be a good therapeutic option because of its relatively high efficacy and acceptable safety profile.

The treatment of NRs with advanced fibrosis, particularly cirrhosis, should be started only in patients with well-compensated liver function and without significant concomitant disease or hematologic disorders. In patients with early-stage, stable liver disease, waiting for IFN-free regimens should be considered. The eventual decision to initiate triple therapy with first-generation PIs for patients with advanced liver disease should be preceded by a careful analysis of the risk factors and, if possible, their elimination (eg, eradication of the foci of infection); additionally, the patient should be educated, with special attention paid to ''alert'' symptoms that indicate the emergence of SAEs. Patient status should be closely monitored during the course of treatment. As shown in our study, a dose reduction in RBV and PegIFN-alpha has a significant influence on treatment outcome in NRs and should be definitely avoided. The best option to improve the outcome in patients with treatment-related hematologic disorders seems to be the usage of hematopoietic growth factors (eg, erythropoietin or granulocyte colony stimulating factor) or blood transfusions to maintain full doses of RBV and/or PegIFN.

In conclusion, we confirmed that reductions of the total planned doses of RBV in NRs or PegIFN-alpha in nonresponders to a previous dual PegIFN-alpha plus RBV regimen during triple therapy containing telaprevir significantly reduces the probability of achieving SVR in patients with advanced liver fibrosis. One way to address this problem might be to provide wide and early access to novel, efficient, and safe interferon-free combinations to treatment-experienced patients, particularly those with liver cirrhosis.

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REFERENCES

1. Jacobson IM, McHutchinson JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med.* 2011;364:2405–2416.
2. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med.* 2011;364:2417–2428.
3. Boccaccio V, Bruno S. Management of HCV patients with cirrhosis with direct acting antivirals. *Liver Int.* 2014;34:38–45.
4. Hezode C, Fontaine H, Dorival C, et al. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS C020-CUPIC)—NCT01514890. *J Hepatol.* 2013;59:434–441.
5. Hézode C, Fontaine H, Dorival C, et al. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. *Gastroenterology.* 2014;147:132–142.
6. Wehmeyer MH, Eissing F, Jordan S, et al. Safety and efficacy of protease inhibitor based combination therapy in a single-center ''real-life'' cohort of 110 patients with chronic hepatitis C genotype 1 infection. *BMC Gastroenterol.* 2014;14:87.
7. Werner CR, Franz C, Egetemeyr DP, et al. Efficacy and safety of telaprevir (TVR) triple therapy in a ''real-life'' cohort of 102 patients with HCV genotype 1: interim analysis after 24 weeks of treatment. *J Viral Hepat.* 2014;21:333–340.
8. Akiyama MJ, Piotrowski JI, Roytman MM, et al. New triple therapy for chronic hepatitis C: real life clinical experience in a community setting. *Hawaii J Med Public Health.* 2013;72:6–13.
9. Colombo M, Fernandez D, Abdurakhmanov P, et al. Safety and on-treatment efficacy of telaprevir: the early access programme for patients with advanced hepatitis C. *Gut.* 2014;63:1150–1158.
10. Castera L, Verignol J, Foucher J, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology.* 2005;128:343–350.
11. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet.* 1997;349:825–832.
12. Poynard T, Yuen MF, Ratziu V, et al. Viral hepatitis C: review. *Lancet.* 2003;362:2095–2100.
13. Poynard T, McHutchinson J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology.* 2002;122:1303–1313.
14. Serpaggi J, Carnot F, Nalpas B, et al. Direct and indirect evidence for the reversibility of cirrhosis. *Hum Pathol.* 2006;37:1519–1526.
15. Pinzani M, Rosselli M, Zuckerman MD. Liver cirrhosis. *Best Pract Res Clin Gastroenterol.* 2011;25:281–290.
16. Lee YA, Friedman SL. Reversal, maintenance or progression: what happens to the liver after a virologic cure of hepatitis C? *Antiviral Res.* 2014;107:23–30.
17. Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol.* 2010;52:562–567.
18. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology.* 2007;45:579–587.
19. Morgan TR, Ghany MG, Kim HY, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology.* 2010;52:833–844.
20. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA.* 2012;308:2584–2593.
21. Pol S, Roberts SK, Andreone P, et al. Efficacy and safety of telaprevir-based regimens in cirrhotic patients with HCV genotype 1 and prior peginterferon/ribavirin treatment failure: subanalysis of the REALIZE phase III study. *Hepatology.* 2011;54:374A–375A.
22. Colombo M, Strasser S, Moreno C, et al. Sustained virological response with telaprevir in 1078 patients with advanced hepatitis C: the international telaprevir access program. *J Hepatol.* 2014;61:976–983.
23. Sulkowski MS, Wasserman R, Brooks L, et al. Changes in haemoglobin during interferon alpha-2b plus ribavirin combination therapy for chronic hepatitis C virus infection. *J Vir Hep.* 2004;11:243–250.
24. McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1—infected patients with chronic hepatitis C. *Gastroenterology.* 2002;123:1061–1069.
25. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med.* 2014;370:211–221.
26. Sulkowski MS, Jacobson IM, Nelson DR. Daclatasvir plus sofosbuvir for HCV infection. *N Engl J Med.* 2014;370:1560–1561.
27. Asselah T, Marcellin P. Direct acting antivirals for the treatment of chronic hepatitis C: one pill a day for tomorrow. *Liver Int.* 2012;32:88–102.
28. de Lemos AS, Chung RT. Hepatitis C treatment: an incipient therapeutic revolution. *Trends Mol Med.* 2014;20:315–321.
29. Lim TR, Tan BH, Mutimer DJ. Evolution and emergence of a new era of antiviral treatment for chronic hepatitis C infection. *Int J Antimicrob Agents.* 2014;43:17–25.
30. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med.* 2014;370:1983–1992.
31. Buti M, Esteban R. Preparing the patient for success: treat or wait? *Dig Liv Dis.* 2013;45(Suppl 5):S332–S336.
32. Van der Meer AJ, Wedemeyer H, Feld JJ, et al. Is there sufficient evidence to recommend antiviral therapy in hepatitis C? *J Hepatol.* 2014;60:191–196.