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Short Communication

Efficacy and tolerability after 24 weeks of treatment with telaprevir, pegylated interferon and ribavirin in cirrhotic HIV–HCV coinfected subjects

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ABSTRACT

Efficacy and tolerability of telaprevir, pegylated interferon and ribavirin combination was assessed in 32 cirrhotic genotype 1 hepatitis C (HCV)–HIV coinfected patients. Undetectability of HCV-RNA was observed in 23/32 (71.9%) patients after 24 weeks. Treatment failure was observed in 9/32 subjects: four of them (45.5%) failed triple therapy due to virological rebound, while 5 patients (55.5%) experienced drug-related side effects driving to treatment interruption. These data suggest that telaprevir-containing triple therapy should be considered for treatment of genotype 1 HCV in HIV coinfected patients with liver cirrhosis, although a close vigilance is required because of potential drug-related side effects.

Since the introduction of combined antiretroviral therapy (cART), AIDS-related morbidity and mortality has decreased among HIV-infected patients (Palella et al., 1998), while end-stage liver disease mostly related with hepatitis C virus (HCV) coinfection has become a leading cause of mortality (Smith et al., 2010; van der Helm et al., 2013). In addition, rates of sustained virological response (SVR) with pegylated interferon (Peg-INF) plus ribavirin among HIV–HCV coinfected patients are less than 30% if patients are infected by HCV genotype 1 (G1) (Torriani et al., 2004). Telaprevir (TVR) is a direct antiviral agent that has shown increased rates of SVR among G1 HCV monoinfected patients, when combined with Peg-INF plus ribavirin, in both naive and pretreated patients (Jacobson et al., 2011; Zeuzem et al., 2011). However, these successful rates are lower in patients with cirrhosis mainly due to the high rates of adverse effects (Hézode et al., 2013). Regarding HIV–HCV coinfected patients, triple therapy with TVR has been also shown to be effective just in naive patients for HCV treatment with low-grade liver fibrosis (Sulkowski et al., 2013). However, studies showing efficacy of this regimen in coinfected subjects with a difficult-to-treat profile (non-CC IL28B genotype, pretreated, advanced fibrosis) are urgently needed. In this sense, only a recent study has shown efficacy of TVR-containing triple therapy in HCV–HIV coinfected patients previously failing dual therapy (Lacombe et al., 2013). Hence, data about this regimen in HIV–HCV coinfected patients with liver cirrhosis are scarce. Thus, the objective of the present observational study was to analyze the 24-weeks efficacy and tolerability of a TVR-containing triple therapy in cirrhotic HIV–HCV coinfected patients.

Abbreviations: cART, combined antirretroviral therapy; HCV, hepatitis C virus; SVR, sustained virological response; Peg-INF, pegylated interferon; G1, genotype 1; TVR, telaprevir; eRVR, extended rapid virological response.

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Between March 2012 and May 2013, an observational multicenter study was begun and included 32 G1 HCV–HIV coinfected patients, recruited from eight centres in Spain, with compensated liver cirrhosis (defined as liver stiffness >14 kPa) starting TVR (1125 mg b.i.d. or 750 mg t.i.d.), Peg-INF (180 μg/week) and ribavirin (dose adjusted according to weight, 15 mg/kg) for treatment of G1 HCV infection. A qualitative PCR amplification was performed for plasma HCV-RNA amplification (COBAS Amplicor, Roche Diagnosis, Barcelona, Spain), with detection limit of 15 IU/ml. Patients were not excluded if modifications of Peg-INF and/or ribavirin dosage or cART switch were performed according to physician decision during the observation period. Intention to treat analysis was performed regarding treatment efficacy; hence, both detectable viral load and therapy interruption due to adverse events were considered as treatment failures.

Baseline characteristics of the 32 cirrhotic patients were: 28 (87.5%) were males, 20 (62.5%) had been previously treated for HCV infection with dual therapy, 19 (59.4%) showed high HCV viral load (>800,000 IU/ml) and 23 (74.2%) showed non-CC IL28B genotype; median [IQR] age was 49 years [47–52], time since HCV diagnosis was 20 years [17–23], MELD stage was 9 [7–11], HCV-RNA viral load was 6.05 $\log_{10}$ IU/ml [5.53–6.42], $CD4^+$ T-cell count was 460 cell/μl [325–735] and liver stiffness was 19,7 kPa [16.3–36.6]. Among 20 patients previously exposed to dual therapy, treatment response was as follows: relapse in 9/20 (45%), partial response in 8/20 (40%) and null response in 3/20 (15%) subjects. It should be noticed that, apart from liver cirrhosis and HIV coinfection, most of the patients presented many negative predictor factors of treatment response (non-CC IL28B genotype, previous non response to dual therapy, high baseline HCV viral load). Indeed 9/32 (28.1%) subjects fulfilled all negative predictor factors of virological response. None of the patients were positive for HBsAg. Regarding the cART for HIV infection combined with triple therapy, 81.25% were receiving two nucleoside reverse transcriptase inhibitors combined with either raltegravir, ritonavir boosted atazanavir or etravirine.

Percentage of patients achieving undetectability of HCV-RNA along the follow up is shown in Fig. 1: 25/32 (78.1%) at week 4 and 23/32 (71.9%) at both 12 and 24 weeks. Additionally, it should be noticed that 22/32 (68.8%) subjects achieved extended rapid virologic response (eRVR: undetectability at both 4 and 12 weeks). As expected, relapsers to previous dual therapy showed higher rates of treatment success. Along the observational period, 9/32 (28.1%) patients did not complete triple therapy: 4 patients experienced absence of significant virological response (confirmed HCV-RNA viral load >1000 IU/ml after 12 weeks), while 4 patients interrupted promptly triple therapy due to drug-related adverse events (major depression, grade 3 rash, severe pancytopenia, unspecific intolerance) and one patient died after 12 weeks due to urinary sepsis. Additionally, 4 patients developed low-grade rash and pruritus, while two patients required admission in hospital due to hepatic encephalopathy and acute pyelonephritis, respectively; study treatment was not stopped in any of them during the observational period. Regarding hematologic disorders, grade 3–4 anemia (haemoglobin <8.0 gr/dl) was observed in just one patient in whom treatment was suspended. Requirements of erythropoietin or packed red blood cells transfusion due to grade 2 anemia (haemoglobin 8.0–10.0 gr/dl) were necessary in 12/32 (37.5%) patients, most of them in the first 12 weeks. On the other hand, grade 3–4 neutropenia (<1000/mm^3) and thrombocytopenia (<50,000/mm^3) was observed in 5 and 4 patients, respectively. No HIV viral rebound was observed in any patient on cART.

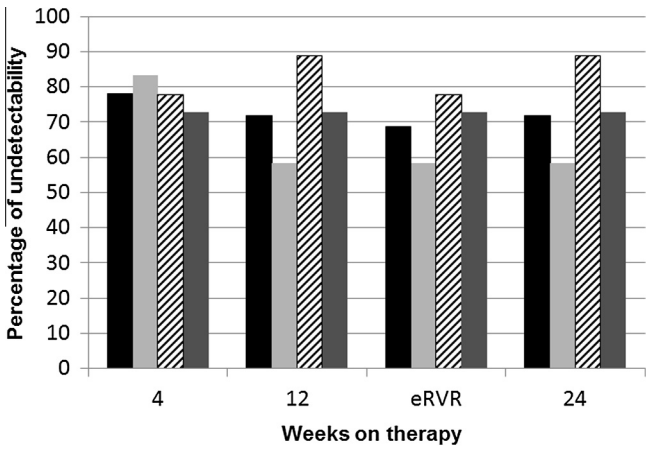

Fig. 1. Percentage of patients achieving HCV-RNA undetectability along the follow up. Black: global population; grey: naive patients; striped: relapsers after dual therapy; dark grey: null and partial responders to dual therapy. eRVR: Extended rapid virological response (undetectability at both 4 and 12 weeks).

Results of this observational multicentre study show a high efficacy and tolerability of TVR-containing triple therapy for G1 HCV infection in HIV–HCV coinfected patients with liver cirrhosis, at least in this interim 24-weeks analysis. Apart from G1, HIV coinfection and cirrhosis, most of the patients included in this analysis combined other negative predictor factors of response: previously failed dual therapy, high HCV-RNA viral load and non-CC IL28B genotype. However, around 70% of these difficult-to-treat patients achieved eRVR, which has been shown to be the best predictor factor of achieving a further sustained virological response (SVR) (Sherman et al., 2011). Moreover, patients with these cumulative negative characteristics would never have been treated for HCV infection with dual therapy due to the low probability of achieving a SVR, but the addition of a direct antiviral agent like TVR allowed a high proportion of them to achieve virological response, although SVR needs to be confirmed.

In accordance with previous data regarding higher toxicity in patients with liver cirrhosis (Hézode et al., 2013), 55.5% of treatment failures were due to therapy discontinuation because of drug-related side effects in patients who were showing an adequate virological response. Additionally, hematologic disorders requiring symptomatic treatment and skin alterations (pruritus and low-grade rash) were observed in a high proportion of patients, although treatment interruption was not necessary. Altogether, these data confirm that a close therapeutic vigilance is a key point during the first weeks of therapy, mainly in cirrhotic patients in whom drug toxicity is increased.

Finally, IL28B polymorphism is a predictor factor of SVR with dual therapy (Ge et al., 2009), but its role in the context of triple therapy is currently discussed and it has even been suggested that IL28B genotype is not associated with SVR in HCV monoinfected patients on TVR-containing triple therapy (Pol et al., 2013). Patients experiencing treatment failure in the present study were both CC and non-CC IL28B carriers, suggesting that IL28B polymorphism impact might be limited in the TVR era. The absence of HIV viral rebound during the observational period suggests that no clinically relevant drug interactions among cART and TVR are present.

In conclusion, this difficult-to-treat G1 HCV population (HIV-coinfected, cirrhotic, mostly non-CC IL28B carriers, mostly with previous failure to dual therapy) showed high rates of virological efficacy after 24 weeks follow up with a TVR-containing triple therapy. Once no therapeutic alternatives are currently available for these patients in order to offer a regimen with less drug-related toxicity, such as Peg-INF free therapy, TVR-containing triple therapy should be considered as the appropriate approach in G1 HCV–HIV coinfected patients with cirrhosis to avoid progression

of liver disease. Nevertheless, a close vigilance of serious adverse events related with therapy is required mainly in the first weeks of treatment.

Conflict of interest

None to declare.

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