Poster 047

Telaprevir in Combination with Peginterferon and Ribavirin in Former Injection Drug Users with Chronic Hepatitis C: Findings of a Prospective, Observational Study

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Introduction

- Approximately 90% of new hepatitis C virus (HCV) infections worldwide, as well as most chronic infections in developed countries, are the result of injection drug use.[1–4]
- HCV infection has been considered difficult to treat in people who inject drugs (PWID) because they may have chaotic lifestyles, HIV or hepatitis B virus (HBV) coinfection, and/or other comorbidities.[5]
- Despite PWID/former PWID representing a substantial 'reservoir' of transmittable HCV, clinicians may be reluctant to treat this population, and there are also concerns about adherence to therapy.[6,7]
- Second-generation direct-acting antivirals (DAAs) for treating HCV are now available in some countries; however, their availability is not universal.
- Telaprevir (TVR), a first-generation DAA, has shown significant improvement in efficacy over peginterferon/ribavirin (Peg-IFN/RBV, PR) alone for the treatment of HCV genotype 1 in non-PWID[8]
  - However, few data exist in active/former PWID since these patients are often excluded from clinical trials.
- Real-life data and information on the impact of therapy on adherence and quality of life are needed in these populations.

Objectives

- This real-life INTEGRATE study (NCT01980290) was the first to examine DAA use in combination with Peg-IFN/RBV in former PWID; this study examined the efficacy, safety and adherence to TVR with Peg-IFN/RBV
  - The effect of HCV treatment on health-related quality of life was also assessed.

Methods

Study Design

- This was a multicentre, observational, single-arm, prospective study.
- Patients received TVR 750 mg every 8 hours (q8h) or 1125 mg twice daily (bid) in combination with weekly Peg-IFN and daily RBV (in accordance with approved local labels); followed by either 12 or 36 weeks of Peg-IFN/RBV alone, depending on local approved recommendations (**Figure 1**)
  - Stopping rules followed local approved labels for TVR.

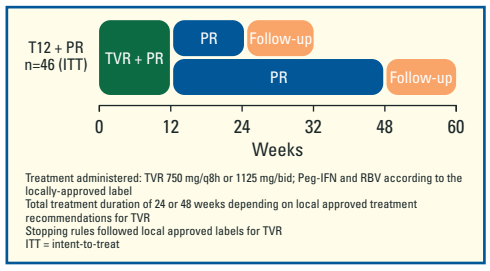

Figure 1. Study Design.

- Patients ≥18 years with a history of injection drug use, had HCV genotype 1, and were HCV treatment-naïve or prior relapsers to dual Peg-IFN/RBV therapy
  - They were on stable opioid substitution therapy and/or were being followed in an addiction centre.
- Patients were excluded if they had received previous DAA therapy for HCV, had history/evidence of decompensated disease, or were coinfected with HIV or HBV.

Study Objectives

- The primary objective was to examine the efficacy of TVR in combination with Peg-IFN/RBV, defined as sustained virologic response (SVR) 12 weeks following the last dose of study medication (SVR12).
- Secondary objectives included:
  - On-treatment virologic response (rapid virologic response [RVR], HCV RNA <25 IU/mL undetectable at Week 4); and extended RVR (eRVR, HCV <25 IU/mL undetectable at Week 4 and Week 12)
  - Treatment failure rates, adherence to treatment, and changes in health-related quality of life, safety.

Study Evaluations

- Efficacy was assessed in the ITT population, and in the efficacy evaluable (EE) population
  - Those excluded from the EE population had a major protocol deviation that plausibly affected effectiveness, or who had a missing follow-up Week 12 HCV RNA assessment.
- HCV RNA levels were obtained on Day 1 (baseline), Week 4, Week 12, Week 24, at the end of Peg-IFN/RBV treatment, and at the end of the follow-up period
  - Most investigators used the High Pure System COBAS® TaqMan (v2.0; Roche) or Abbott RealTi*m*e HCV assays to quantify HCV RNA
    - 86% of the assays used had a lower limit of quantification of 25 IU/mL.
- Virologic breakthrough was defined as: (i) a >1 $\log_{10}$ increase in HCV RNA from the lowest level reached, if the lowest level was >25 IU/mL; or (ii) in patients who previously had <25 IU/mL (detectable/undetectable), if a HCV RNA value of >100 IU/mL was obtained.
- Relapse was defined as having <25 IU/mL, undetectable at end of treatment (EOT) and then having:
  - HCV RNA detectable during the follow-up phase
  - Or not achieving SVR12 (defined as <25 IU/mL, undetectable 12 weeks after the last planned dose of study medication).
- Safety and tolerability of TVR were monitored throughout the study (ITT population).

Adherence to HCV Treatment

- Adherence to TVR, Peg-IFN and RBV was assessed using M-MASRI questionnaire[9]
  - Patients were asked to report the number of doses taken in the preceding 30 days to generate a self-reported percentage (received/total).

Patient-reported Quality of Life

- The EQ-5D™ questionnaire assessed the impact of treatment on quality of life[10]
  - EQ-5D consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (each rated as: no problems; some/moderate; or extreme)
    - A standard visual analogue scale was used to record a patient's overall quality of life, with a score of 100 the best possible outcome.
- The Hospital Anxiety and Depression Scale (HADS) involved a 14-item scale, 7 relating to anxiety, 7 to depression (each item scored 0 to 3 [3 indicating greater likelihood of anxiety or depression])[11] over a recall period of 1 week
  - A total score of 0–7 = normal; 8–10 = mild; 11–14 = moderate; 15–21 = severe.
- The AUDIT questionnaire, consisting of 10 questions, assessed quantity and frequency of alcohol use[12]
  - A score of ≥8 was associated with harmful or hazardous drinking.
- Both the EQ-5D and HADS questionnaires were completed on Day 1, Week 4, Week 12, Week 24, EOT and end of follow-up.
- The AUDIT questionnaire was completed on Day 1, Week 12, EOT, and end of follow-up.

Results

Patient Disposition and Baseline Characteristics

- A total of 46 patients were enrolled in the study and received HCV treatment with Peg-IFN/RBV + TVR (ITT population)
  - Of these patients, 87% (40/46) were male and 91% (42/46) were white.
- Overall, 35% (16/46) of patients had no-to-mild fibrosis (METAVIR F0–F1); most patients were treatment naïve (94%, 43/46).
- Most patients had HCV genotype subtype 1a (80%, 37/46); 15% (7/46) had HCV genotype 1b; two patients had an unspecified genotype (**Table 1**).

Table 1. Baseline Demographics and Disease Characteristics.

	Treatment naïve (n=43)	Prior relapsers (n=3)	Total (N=46)
Median age, years (range)	43 (28–57)	47 (44–56)	44 (28–57)
Age ≤45 years, n (%)	27 (63)	1 (33)	28 (61)
White, n (%)	39 (91)	3 (100)	42 (91)
Male, n (%)	37 (86)	3 (100)	40 (87)
Body mass index (kg/m²), median (range)	25 (17–36)	26 (22–27)	25 (17–36)
HCV subtype, n (%)			
1a	34 (79)	3 (100)	37 (80)
1b	7 (16)	0	7 (15)
Other (unspecified)	2 (5)	0	2 (4)
Fibrosis stage, n (%)			
F0–1	15 (35)	1 (33)	16 (35)
F2	7 (16)	0	7 (15)
F3	4 (9)	1 (33)	5 (11)
F4	7 (16)	0	7 (15)
Unknown	10 (23)	1 (33)	11 (24)
Baseline VL ≥800000 IU/mL, n (%)	26 (61)	2 (67)	28 (61)
Patients on substitution therapy	39 (91)	3 (100)	42 (91)
Methadone	30 (70)	2 (67)	32 (70)
Buprenorphine	9 (21)	1 (33)	10 (22)

IL28B genotyping results were only available in 19 (41.3%) patients: 17.4% were *IL28B* CC; 19.6% CT; 4.3% TT

Efficacy

- Overall, 54% (25/46) of the patients in the ITT population achieved SVR12 (**Figure 2**)
  - 24/43 (56%) of treatment-naïve patients achieved an SVR
  - One of the three prior relapse patients achieved an SVR.
- RVR was achieved by 83% (38/46) of patients
  - 72% (33/46) achieved eRVR, including 31/43 treatment-naïve patients and two of three prior relapsers to Peg-IFN/RBV
    - Of the 33 patients who achieved eRVR, 24 (73%) achieved SVR.

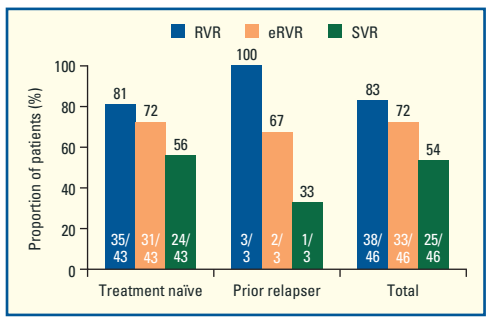

Figure 2. Virologic Response (Defined as <25 IU/mL) to TVR + Peg-IFN/RBV in the ITT Population Throughout the Study Period.

- Of the 21 patients who did not achieve SVR12, one experienced relapse, and one virologic breakthrough
  - 19 patients had: either missing data during the follow-up Week 12 window, or HCV RNA >25 IU/mL at the SVR timepoint but had neither relapse nor viral breakthrough
  - 17/19 had missing data at follow-up Week 12; 2/19 had HCV RNA >25 IU/mL.
- In the EE population, 25/34 (74%) patients achieved SVR12:
  - 24 patients were treatment naïve; one was a prior relapser.
- The main reason for patients in the EE population not achieving SVR12 was 'other' (20.6%)
  - These patients had missing data at the follow-up Week 12 window or had HCV RNA >25 IU/mL at the SVR timepoint, but neither had relapse nor viral breakthrough.

Adherence to Treatment

- High adherence rates were maintained throughout the study period
  - A median of 100% adherence was reported at Week 4 and Week 12 based on 32 and 22 responses, respectively (**Figure 3**)
  - Both mean TVR treatment adherence until Week 12, and Peg-IFN/RBV adherence until EOT exceeded 90%.

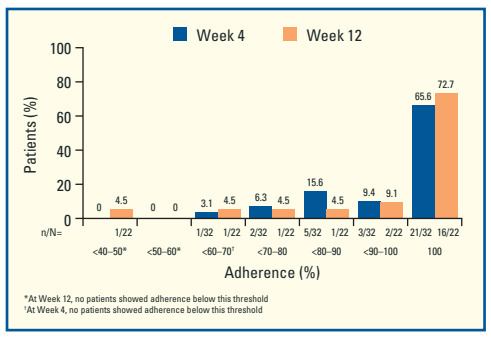

Figure 3. TVR Treatment Adherence as Determined by the M-MASRI Questionnaire.

Health-related Quality of Life

- Figure 4 shows the health-related quality of life scores over time.
- HCV treatment did not negatively impact overall quality of life (**Figure 4a**), levels of anxiety and depression (**Figure 4b**), or alcohol intake (**Figure 4c**).

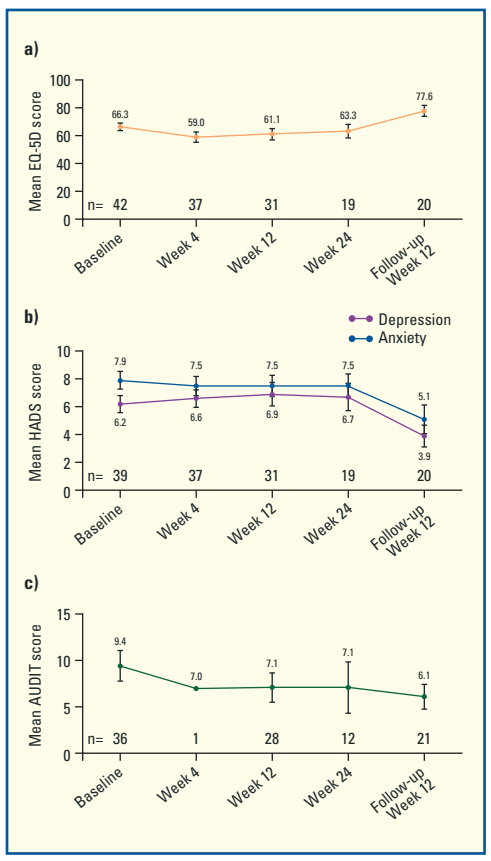

Figure 4. Summary Data (Mean ± 95% Confidence Interval) of a) EQ-5D Health Outcome Questionnaire, b) HADS Depression and Anxiety Scales and c) AUDIT Score.

Safety

- Overall, 70% (32/46) of patients had at least 1 adverse event (AE) considered possibly related to TVR
  - The most common TVR-related AEs reported were anaemia and thrombocytopenia (**Table 2**).
  - Of the 15/46 (33%) patients who experienced TVR-related anaemia, eight received no iron-based drugs, erythropoetins or blood transfusion; six had a blood transfusion (n=1 also received platelets), and one received erythropoietin.
- Serious AEs were reported by 24% (11/46) of patients.
- Four patients (9%) discontinued TVR due to TVR-related AEs.
- No new safety concerns, drug–drug interactions or deaths were reported.

Table 2. Safety of TVR + Peg-IFN/RBV in the INTEGRATE Study.

n (%)	Total (N=46)
Patients with any events considered at least possibly related to TVR	32 (70)
Commonly-reported AEs*	
Anaemia SSC	15 (33)
Thrombocytopenia	11 (24)
Rash SSC	7 (15)
Fatigue	7 (15)
Leucopenia	7 (15)
Pruritus SSC	7 (15)
All serious AEs	11 (24)
Serious AEs considered at least possible related to TVR	2 (4)
AEs Grade ≥2 thought to be related to TVR	26 (57)
Treatment discontinuations related to TVR	4 (9)

*AEs considered possibly related to TVR in ≥15% of the ITT population
SSC = special search category

Conclusions

- In this study of former PWID, 54% of patients achieved SVR12 following treatment with TVR + Peg-IFN/RBV; 8/46 patients were lost to follow-up and were, therefore, counted as nonresponse.
- In the EE population, 74% of patients achieved SVR12
  - This is in line with data from the TVR registration trials in treatment-naïve patients[13,14]
- High rates of self-reported adherence to TVR were observed throughout the treatment phase.
- HCV treatment did not negatively impact overall health-related quality of life, levels of anxiety and depression, or alcohol intake.
- The safety profile of TVR-based triple therapy in this population was similar to that reported in the non-PWID population, with anaemia being the most common AE
  - No drug–drug interactions were reported.
- Overall, the findings indicate that protease-inhibitor-based therapy is suitable for this clinically important population in reducing transmission of HCV, especially in settings where IFN-free therapies are not yet available.

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