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Early Clearance of HCV RNA in HCV Genotype 1 Treatment-naïve Patients Treated with Telaprevir, Peginterferon and Ribavirin: Pooled Analysis of the Phase 3 Trials ADVANCE and ILLUMINATE

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ABSTRACT

- **Background:** Phase 3 trials have demonstrated that addition of telaprevir to currently approved regimens containing peginterferon alfa and ribavirin significantly increased treatment response rates and permitted the majority of patients (pts) to shorten treatment duration to 24 wks.
- **Methods:** Pooled analysis of pts enrolled in two Phase 3 trials (ADVANCE/ILLUMINATE) was performed. Both trials included a regimen of telaprevir ((T) 750 mg po q8h 12 wks), peginterferon alfa-2a (P) SQ q wk + weight-based ribavirin (R) (T12PR). Treatment duration (24 vs. 48 wks) was determined using a response-guided decision tree based upon presence or absence of extended rapid virologic response (eRVR, HCV RNA undetectability at wks 4 and 12). HCV RNA was evaluated using the TaqMan assay (limit of quantification 25 IU/ml).
- **Results:** 903 pts, treated with T12PR, were compared to PR ((N=361) ADVANCE only). The pooled T12PR group was 60% male, 83% Caucasian with a mean age of 48 years. 80% of pts had baseline HCV RNA ≥ 800,000 IU/ml, 25% had advanced fibrosis (F3/F4). At wks 1, 2, and 4, 6% (58/903), 28% (251/903) and 70% (635/903) of T12PR pts had undetectable HCV RNA vs. 2% (7/361), 5% (17/361), 9% (34/361) in PR. HCV RNA undetectability at wks 1, 2 and 4 were associated with eRVR and sustained virologic response (SVR) (Table). The most common AEs during overall treatment phase were fatigue, pruritus, and nausea. Overall discontinuation rates of all study drugs due to AEs during telaprevir treatment phase were 7% and 4% for T12PR and PR, respectively.
- **Conclusion:** Addition of telaprevir to PR led to rapid HCV RNA decline in approximately 3-, 6- and 8-fold more patients at Weeks 1, 2, and 4, respectively, compared to PR alone. Early HCV RNA decline was associated with SVR. Overall adverse event profile was similar to that previously observed; rates of discontinuation of study regimen were low.

INTRODUCTION

- Telaprevir (TVR, T) is an orally bioavailable, specifically targeted antiviral drug for hepatitis C virus (HCV) that potently and selectively inhibits the HCV NS3•4A protease.[1,2]
- TVR in combination with peginterferon and ribavirin (PR) has been studied in treatment-naïve patients and improved sustained virologic response (SVR) rates, compared with PR alone.[3,4,5]
- ADVANCE was a randomized, placebo-controlled, Phase 3 clinical trial that evaluated efficacy and safety of TVR in combination with PR in chronic HCV genotype 1-infected treatment-naïve patients.[5]
- ILLUMINATE was an open-label, randomized, non-inferiority Phase 3 clinical trial that evaluated efficacy and safety of 24 weeks of TVR-based treatment versus 48 weeks in chronic HCV genotype 1-infected treatment-naïve patients who achieved extended rapid virologic response (eRVR, undetectable HCV RNA at weeks 4 and 12).[6]
- We studied HCV RNA levels at early viral timepoints and its relationship to SVR in this retrospective pooled analysis of ADVANCE and ILLUMINATE patients.

METHODS

Study Design

Figure 1A: Study Design of ADVANCE Trials

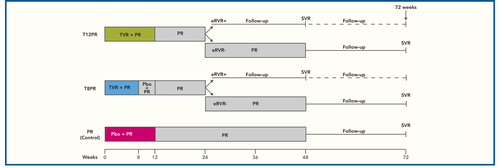
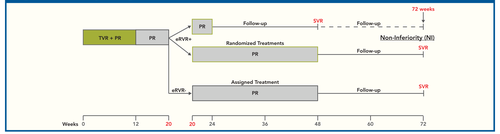


Figure 1B: Study Design of ILLUMINATE Trials



Patient Population

- Treatment-naïve patients infected with genotype 1 chronic HCV were enrolled:
  - 123 centers in North America, Europe, Argentina, Australia and Israel in ADVANCE
  - 74 centers in the United States and Europe in ILLUMINATE
- Key eligibility criteria in patients:
  - 18-70 years of age
  - Evidence of chronic hepatitis by liver biopsy within 1 year of screening for the study
  - Patients with compensated liver cirrhosis were included.

Efficacy Assessments

- Plasma HCV RNA assessment by Roche COBAS TaqMan® HCV test (Version 2.0) lower limit of detection 25 IU/mL; HCV RNA values lower than 25 IU/milliliter were reported as either less than 25 IU/milliliter detectable or undetectable.
- HCV RNA levels were measured on Day 1 and at Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, 36, 40, 48, follow-up visits 4 weeks after end of treatment, and at Weeks 60 and 72.

Safety Assessments

- Safety and tolerability were assessed by monitoring adverse events (AEs), vital signs, laboratory test abnormalities and electrocardiogram findings.

Pooled Analysis

- Patients who received 12 weeks telaprevir with either a total of 24 weeks or 48 weeks of PR were pooled from ADVANCE and ILLUMINATE (T12PR) and compared to patients who received PR (ADVANCE).
- eRVR, undetectable at EOT, and SVR in T12PR patients who achieved Weeks 1, 2, and 4 HCV RNA undetectability were analyzed versus PR.
- Adverse events and discontinuation rate due to adverse events were also compared in T12PR versus PR.

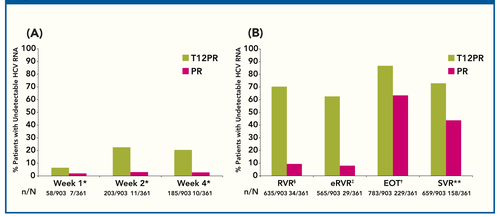
RESULTS

Table 1: Baseline Characteristics and Demographics

	T12PR (N=903)	PR (N=361)
Gender, n (%)		
Male	539 (60)	211 (58)
Race, n (%)		
Caucasian	752 (83)	318 (88)
Black	99 (11)	28 (8)
Ethnicity, n (%)		
Hispanic or Latino	89 (9)	38 (11)
Age, median (range)	50 (19-70)	50 (18-69)
BMI, median (range)	27 (18-54)	26 (17-48)
Baseline HCV RNA $\log_{10}$ IU/mL, n (%)		
≥800,000 IU/mL	726 (80)	279 (77)
<800,000 IU/mL	177 (20)	82 (23)
HCV genotype, n (%)		
1a	604 (67)	208 (58)
1b	298 (33)	151 (42)
1 (subtype unknown)	4 (<1)	2 (1)
Liver disease status, n (%)		
No or minimal, and portal fibrosis	681 (75)	288 (80)
Bridging fibrosis	140 (16)	52 (14)
Cirrhosis	82 (9)	21 (6)

BMI = body mass index; Genotype determined by TRUGENE genotypic assay (Siemens Medical Solution Diagnostics).

Figure 2: Patients with Undetectable HCV RNA over Time



*Patients who first became undetectable for HCV RNA at respective week. Week 3 timepoint was assessed but is not shown here. †RVR = rapid viral response, RVR includes all patients who had undetectable HCV RNA at week 4; ‡eRVR = extended rapid viral response; §EOT = end of treatment; **SVR = sustained viral response

- 6%, 22%, and 20% of T12PR patients had undetectable HCV RNA at Week 1, Week 2, and Week 4, respectively, compared to 2%, 3%, and 3% of patients in PR, respectively (Figure 2A).
- 70%, 63% and 73% of T12PR patients achieved RVR, eRVR, and SVR compared to 9%, 8%, and 44% of PR patients, respectively (Figure 2B).

Figure 3: Patients with eRVR According to Week 1, Week 2, or Week 4 HCV RNA Undetectability

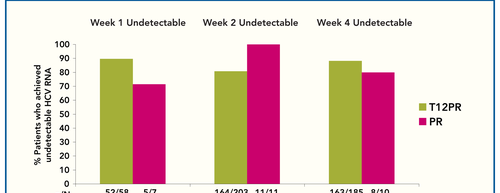


Figure 4: Patients with Undetectable HCV RNA at EOT According to Week 1, Week 2, or Week 4 HCV RNA Undetectability

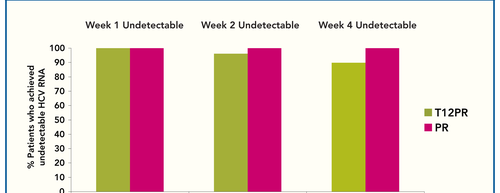


Figure 5: Patients who Achieved SVR According to Week 1, Week 2, or Week 4 HCV RNA Undetectability

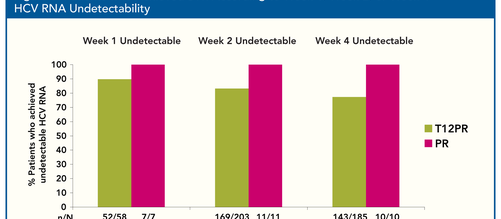


Table 2: Rates of On-treatment Virologic Failure and Relapse in Patients who had Undetectable HCV RNA at Week 1, Week 2, and Week 4

n/N (%)	T12PR (N=903)	PR (N=361)
Week 1:		
Virologic Failure*	0/58 (0)	0/7 (0)
Relapse	0/58 (0)	0/7 (0)
Week 2:		
Virologic Failure*	5/203 (2)	0/11 (0)
Relapse	6/195 (3)	0/11 (0)
Week 4:		
Virologic Failure*	13/185 (7)	0/10 (0)
Relapse	15/166 (9)	0/11 (0)

*Patients who met virologic stopping rule (Week 4 HCV RNA > 1000 IU/mL patients receiving telaprevir-based regimen were to discontinue telaprevir and continue PR, Week 12 HCV RNA < 2 $\log_{10}$ decrease compared to baseline, patients were to discontinue all study drugs, or Week 24 – 36 Detectable HCV RNA > 10 IU/mL patients were to discontinue all study drugs) or had detectable HCV RNA at end of completed treatment.

- Overall 7% (66/903) of T12PR patients experienced virologic failure versus 32% (115/361) of PR patients.
- Overall 8% (64/903) of T12PR patients experienced relapse versus 28% (64/361) of PR patients (Table 2).

Safety Analysis

Table 3: Most Common Adverse Events in Greater than 25% of Patients in the Overall Treatment Phase

Adverse events, n (%)	T12PR (N=903)	PR (N=361)
Fatigue	576 (64)	206 (57)
Pruritus	**454 (50)**	**131 (36)**
Nausea	**409 (45)**	**112 (31)**
Headache	352 (39)	142 (39)
Anemia	**347 (38)**	**70 (19)**
Rash	**335 (37)**	**88 (24)**
Insomnia	299 (33)	111 (31)
Influenza-like Illness	243 (27)	101 (28)
Diarrhea	266 (29)	80 (22)

- Most common adverse events reported in T12PR patients ≥10% difference from PR patients were pruritus, nausea, anemia, and rash (in bold, Table 3).
- During the telaprevir treatment phase, 7% and 4% of T12PR and PR patients discontinued all study drugs including 1% and 1% of T12PR and 0% and 1% of PR patients due to rash and anemia events, respectively.
- During the overall treatment phase, 14% and 7% of T12PR and PR patients discontinued all study drugs including 2% and 2% of T12PR and 0% and 1% of PR patients due to rash and anemia events, respectively.

SUMMARY AND CONCLUSIONS

- More patients were undetectable for HCV RNA at early timepoints when treated with a telaprevir-based regimen.
  - 6%, 22%, and 20% of T12PR patients had first undetectable HCV RNA at Week 1, Week 2, and Week 4, respectively.
  - 2%, 3%, and 3% of patients treated with peginterferon alfa-2a/ribavirin alone had first undetectable HCV RNA at Week 1, Week 2, and Week 4, respectively.
- Patients treated with a telaprevir-based regimen, who had early HCV RNA undetectability, had higher sustained viral response rates
  - 90% of patients, with undetectable HCV RNA at Week 1, achieved a sustained viral response rate compared to 83% and 77% in Week 2 and Week 4 first undetectable HCV RNA patients.
- Regardless of treatment regimen, patients with early HCV RNA undetectability had higher sustained viral response rates, however, as stated above, fewer patients treated with peginterferon alfa-2a/ribavirin alone had undetectable HCV RNA at early viral timepoints compared to patients who received telaprevir-based regimen.
- A majority of patients treated with a telaprevir-based regimen received 24 weeks of total treatment while all patients treated with peginterferon alfa-2a/ribavirin alone received 48 weeks of total treatment.[5,6]
- There were low discontinuation rates of all study drugs due to rash and anemia events during the telaprevir treatment phase with overall discontinuation rates due to adverse events of 7% and 4% in T12PR and peginterferon alfa-2a/ribavirin patients respectively.

Author Disclosures

KE Sherman has received institutional Grants/Research support: Anadys Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, Merck, Roche, Schering-Plough, Vertex Pharmaceuticals; Advisory or Review Committee Member: Bristol-Myers Squibb, GlaxoSmithKline, Merck, Pfizer, Valeant Pharmaceuticals, Vertex Pharmaceuticals; **GT Everson** has received grants/research support: Abbott, Bristol-Myers Squibb, Conatus Pharmaceuticals, Gilead Sciences, GlobeImmune, Human Genome Sciences, Merck, Novartis, Pfizer, Roche, Schering-Plough, Tibotec, Vertex Pharmaceuticals; Advisory or Review Committee Member: Abbott, Bristol-Myers Squibb, Gilead Sciences, Merck, Pfizer, Roche, Vertex Pharmaceuticals; **IM Jacobson** has received consulting and lecture fees from Abbott, Anadys Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlobeImmune, Human Genome Sciences, Novartis, Pharmasset, Pfizer, Roche/Genentech, Sanofi–Aventis, Schering- Plough/Merck, Tibotec, Vertex Pharmaceuticals and Zymogenetics; and Grant/Research Support from Anadys Pharmaceuticals, Boehringer Ingelheim, Gilead Sciences, GlobeImmune, Human Genome Sciences, Novartis, Pharmasset, Roche/Genentech, Schering- Plough/Merck, Tibotec and Vertex Pharmaceuticals; **AM Di Bisceglie** has received consulting fees from Abbott, Anadys Pharmaceuticals, Bristol Myers Squibb, GlobeImmune, Idenix, Pharmasset, Roche/Genentech and Vertex Pharmaceuticals; and Grant/Research Support from Bristol Myers Squibb, Gilead Sciences, GlobeImmune, Idenix, Roche/Genentech and Vertex Pharmaceuticals; **DR Nelson** has received consulting/lecture fees: Bayer HealthCare, Biolex, Roche; Grants/Research Support: Abbott, Anadys Pharmaceuticals, Bayer HealthCare, Bristol-Myers Squibb, Gilead Sciences, Human Genome Sciences, Merck, Novartis, Roche, Vertex Pharmaceuticals; Advisory or Review Committee Member - Abbott, Bayer HealthCare, Biolex, Gilead Sciences, GlaxoSmithKline, Merck, Roche; **L Bengtsson, N Adda, RS Kauffman, and CI Wright** are current stock owners and employees of Vertex Pharmaceuticals; **S Zeuzem** has received consulting and lecture fees from Abbott, Achillion, Anadys Pharmaceuticals, Bayer, Bristol-Myers Squibb, Gilead Sciences, Human Genome Sciences, Novartis, Pharmasset, Roche/Genentech, Santaris, Schering-Plough/Merck, Tibotec and Vertex Pharmaceuticals

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Acknowledgements

We thank all of the patients, study coordinators, CROs, and investigators who participated in the ADVANCE and ILLUMINATE studies. Medical writing and editorial support was provided by Mrudula Donepudi, PhD, graphic design support was provided by Jonathan Kirk, both employees and stock owners of Vertex Pharmaceuticals Incorporated.

Supported by Tibotec, a division of Janssen-Cilag Inc. and Vertex Pharmaceuticals Incorporated