Resistance Profile Of ABT-333 And Relationship To Viral Load Decrease In Patients Treated In Combination With Peg-interferon And Ribavirin For 28 Days.

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Background

ABT-333 is a non-nucleoside HCV NS5B polymerase inhibitor with potent in vitro activity against all known genotypes of HCV. The resistance profile predicted for monotherapy in vitro is similar to that seen with filibuvat, another non-nucleoside HCV NS5B polymerase inhibitor. The predicted resistance phenotype to 300 mg BID was 1000 nM, for 600 mg BID 100 nM, and for 1200 mg QD 10 nM. No significant difference between groups dosed with ABT-333 was noted.

In Vivo Response To Treatment

Phenotypic and Genotypic Summary of Mixed Populations

Samples taken before dosing, or at days 5, 10, 14, 17, 24 or 28 after the initial dose were analyzed for viral load. ABT-333 EC50 against HCV GT 1b GT 1a isolates cloned into replicons, and for the presence of variants previously demonstrated to confer resistance to ABT-333.

Average viral load decrease of 3.7 log10 across ABT-333 dose groups. Close agreement was noted between the five amino acid positions.

In vitro resistance to ABT-333 was measured in a subgenomic replicon, followed determination of EC50 in a transient transfection assay.

Resistant variants emerged on treatment with ABT-333, but the emergence of resistance did not appear to impact continued response to therapy, suggesting that resistant variants are still susceptible to the combination of ABT-333 + pegIFN/RBV.

Methods

• Baseline HCV RNA, mean (SD) log10 IU/mL 6.47 (0.27) 6.29 (0.48)
• Average viral load decreased of 3.7 log10 across ABT-333 dose groups
• Close agreement was noted between the five amino acid positions

In Vitro Resistance To ABT-333

Summary and Conclusions

• Resistant variants emerged on treatment with ABT-333, but the emergence of resistance did not appear to impact continued response to therapy, suggesting that resistant variants are still susceptible to the combination of ABT-333 + pegIFN/RBV.
• Baseline and maximum EC50 observed during the treatment period (beginning and end of line)

Clonal Sequence Analysis

Summary

• 37 of 40 clinical isolates (93%) contained at least one significant resistance variant.
• Variants were uniformly distributed between the five amino acid positions.
• Variants noted at later time points at amino acids 414, 448, 556, 559. 414M/T increased EC50 to >3000 nM.
• Variants were relatively uniformly distributed between the five amino acid positions.
• Two days of monotherapy followed by 26 days of combination with pegIFNα + RBV for 26 days.
• Doses of ABT-333 used were 300 mg BID, 600 mg BID and 1200 mg QD.
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