ABT-530, an HCV NS5A Inhibitor With Potent Antiviral Activity and High Genetic Barrier to Resistance

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ABSTRACT

• To characterize the HCV NS5A inhibitors are proven therapeughtic potential of ABT-530 in HCV replicon cells
• To determine the drug-resistant replicon variants that emerged during selection and the gene used to determine an improved virological profile

BACKGROUND

- HCV NS5A inhibitors are proven therapeutic agents in treating chronic HCV infection
- First generation NS5A inhibitors (e.g., daclatasvir, ledipasvir) and ABT-267
- Demonstrated potent antiviral activity against HCV genotype 1 but may have lower activity against genotypes 2, 3, and/or 6
- Have common signature resistance-associated variants, e.g., mutations at amino acid positions 28, 30, 31, and 93, that confer high level of resistance
- ABT-530 is a next generation HCV NS5A inhibitor that has an improved virological profile compared to other NS5A inhibitors in clinical development
- It demonstrates potent activity against HCV genotypes 1–6 in vitro
- It is active in vitro against commonly observed variants that are highly resistant to other NS5A inhibitors
- It has entered phase II clinical development and will be studied in combination with other direct-acting antivirals in patients chronically infected with HCV of different genotypes

OBJECTIVES

- To characterize the in vitro antiviral activity and genotypic coverage of ABT-530 in HCV replicon cells
- To determine the in vitro resistance and cross-progression as well as the genetic barrier to resistance of ABT-530

METHODS

- Huh-7 cells with a hA777 or hB192 subgenomic replications, or 1b-Cons based chimera subgenomic replicons containing domain I of the NS5A gene from genotypes 2a, 2b, 3a, 4a, 5a, and/or 6a, were used to determine antiviral activity and to select for drug-resistant replicon variants
- The genetic barrier to resistance in HCV replicons with genotypes 1–6 NS5A was measured in resistant colony selection assays using concentrations at various multiples of the EC50 value of ABT-530 in the respective replicon
- Drop-resistant replicon variants that emerged during selection were identified by sequencing of NS5A gene, and phenotypic analyses of the variants were performed by introducing the variants into their corresponding wild-type replicons and testing them in transient transfection assays

RESULTS

- ABT-530 is a potent HCV inhibitor with EC50 values in the low picomolar range across all genotypes
- Cytotoxicity (TD50): >32 000 000 pM in Huh-7 cells; therapeutic index: >1x10^10-fold
- ABT-530 is more potent across HCV genotypes 1–6 than other NS5A inhibitors in clinical development

• ABT-530 selected very few or no resistant colonies in HCV genotype 1a replicons, and no colonies in genotype 1b HCV replicons

- ABT-530 is highly active against common genotypes 2–6 NS5A resistance-associated variants

- ABT-530 is highly active against common genotype 1 NS5A resistance-associated variants

- ABT-530 is being developed for use in combination with other direct-acting antivirals in patients chronically infected with HCV of different genotypes

CONCLUSIONS

- ABT-530 is a next generation HCV NS5A inhibitor with a superior in vitro virological profile compared with other NS5A inhibitors currently in clinical development
- It displays potent and similar activity against genotypes 1–6
- It exhibits a high genetic barrier to resistance in genotypes 1–6
- It retains high levels of potency against clinically important resistance variants selected by other NS5A inhibitors in HCV genotypes 1–6
- Of note, ABT-530 is highly active against Y93 variants in genotypes 1 and 3a that confer high levels of resistance to other NS5A inhibitors

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REFERENCES

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