

Meta-analysis Across Adefovir Clinical Trials Demonstrates the Absence of Novel Adefovir-Associated Mutations and Confirms the Role of the rtA181V and rtN236T Mutations in HBV Polymerase in Association with Virologic Failure

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Introduction

- HBV resistance mutations have been identified for all approved oral antiviral agents used in the treatment of chronic hepatitis B (lamivudine, adefovir dipivoxil, and entecavir)
- The rtA181V and rtN236T mutations have been associated with long-term adefovir dipivoxil (ADV) treatment
- Recent reports have proposed that other mutations in HBV polymerase may be associated with ADV resistance

Background

- Virologic outcomes across ADV clinical studies have been defined based on three criteria:
 - Genotypic Resistance Mutations (M) = selection of genotypic changes at critical positions rtA181V and/or rtN236T of HBV polymerase (POL) regardless of HBV DNA level and ALT outcomes
 - Virologic Resistance VR = genotypic resistance and virologic rebound (confirmed $\geq 1 \log_{10}$ copies/mL increase in HBV DNA from nadir) and/or having never achieved HBV DNA suppression $< 3 \log_{10}$ copies/mL
 - Clinical Resistance (M + VR + ALT) = genotypic resistance along with virologic resistance and ALT elevations (ALT $> 1 \times$ ULN after normalizing ALT)
- Genotypic resistance to ADV emerges slowly (0% at 1 year, 29% at 5 years) with a cumulative probability of virologic resistance of 20% at 5 years¹

Objectives

- A meta-analysis of baseline (BL) and on treatment samples from patients across four clinical studies was conducted to:
 - Confirm the role of the rtA181V and rtN236T mutations in clinical resistance to adefovir dipivoxil
 - Screen for and identify other potential ADV-associated resistance mutations

Methods

- Patients from the following studies who completed at least 48 weeks of therapy with ADV 10 mg were included in analysis
 - GS-412 (extension), HBeAg positive and negative, naïve
 - GS-435, HBeAg positive and negative, LAM experienced
 - GS-437, HBeAg positive, naïve
 - GS-438, HBeAg negative, naïve
- Changes in HBV POL from baseline were determined for the last available genotype for each patient with detectable HBV DNA while still on study medication
- Conserved sites were defined as those with only one amino acid observed in the baseline population (n = 853)
- Polymorphic positions defined as those with multiple amino acids observed in the baseline population
- McNemar's Exact test was used to screen paired data (collected at BL and on treatment) for each patient with paired samples across all 4 studies. The % of patients with a switch from consensus amino acid at BL to non-consensus amino acid while on treatment was compared to the % of patients with a switch from non-consensus amino acid at BL to consensus amino acid while on treatment for each POL position with ≥ 1 patient with a switch (n=97).
- p-values used to test for significance were $p < 0.05$ [no adjustment for multiple comparisons] or $p < 0.0005$ [Bonferroni adjustment for testing multiple POL positions with changes]

Results

Table 1. Patients Included in Meta-analysis

Study	Patient Population	N Evaluated	Rebound ^a	Not suppressed ^b	Total w/ paired Genotypes	Average Weeks on ADV
412 (Ext)	eAg +/-	39	9	7	16	99 ± 55
437	eAg +	309	44	68	94	134 ± 98
438	eAg -	183	30	11	38	148 ± 83
435	OLT, LAM-R, eAg +/-	467	8	65	24	99 ± 37
Total	All	998	91	151	172	129 ± 87

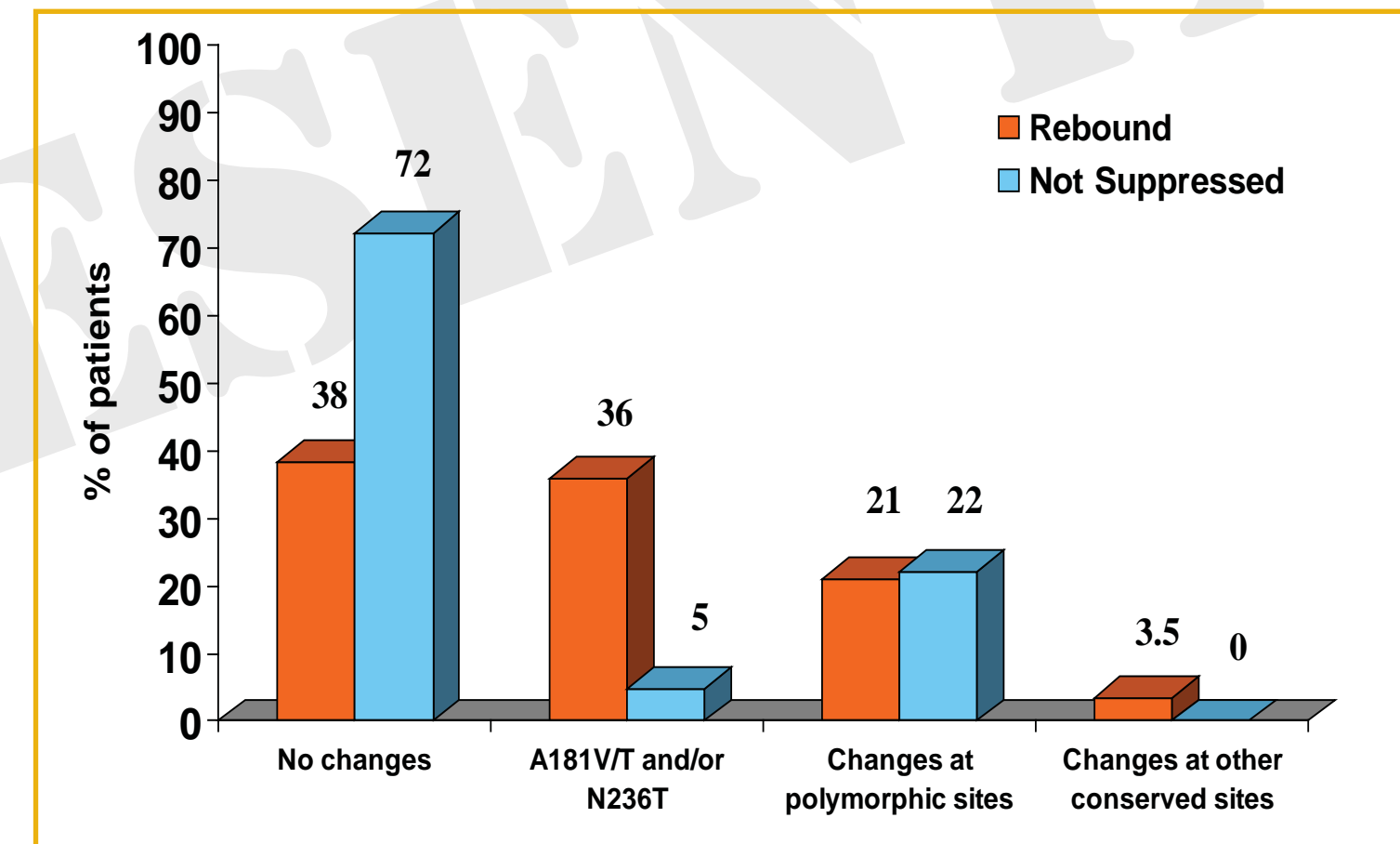
a. Rebound = confirmed $> 1 \log_{10}$ increase in serum HBV DNA from nadir (includes patients who did not achieve HBV DNA < 1000 copies/mL)
b. LOQ = 1000 copies/mL

Table 2. Summary of Genotypic Changes in Patients with Detectable HBV DNA

Population	No mutations	A181V/T and/or N236T ^a	Changes at polymorphic sites	Changes at other conserved sites ^b
n=172	95 (55.2%)	35 (20.3%)	37 (21.5%)	3 (1.7%)

a. With or without changes at polymorphic sites
b. Without A181V or N236T, one each S185T/Y327S, V208I, L180M/M204V; none of the POL positions involved was statistically significant at the $p < 0.05$ or $p < 0.0005$ level

Figure 1. Summary of Genotypic Changes in Patients with Rebound and Not Suppressed



- Patients with HBV DNA rebound were almost eight times more likely to develop ADV-associated mutations at positions rtA181 and/or rtN236 than patients who did not rebound
- Polymorphic changes occurred with similar frequency between both groups and were not statistically associated with a specific amino acid change

Conclusions

- No ADV resistance mutations (rtA181V and/or rtN236T) were observed in the first 48 weeks of therapy
- No changes in HBV POL at positions other than rtA181 and rtN236 were significantly associated with failure on ADV therapy when adjusting for multiple comparisons ($p < 0.0005$)
 - Mutations at POL positions rtN236T and rtA181V were significant by themselves
 - rtA181T mutation was not significant by itself
- Patients who had HBV DNA rebound were more likely to develop adefovir-associated mutations than patients who did not rebound (36% vs. 5%)

References & Disclosure

1. Borroto-Esoda et al. EASL 2006

DISCLOSURE: Authors have financial relationships within the last 12 months relevant to the presentation with Gilead Sciences, Inc.