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Clinical Risk Factors for Hypersensitivity Reactions to Abacavir: Retrospective Analysis of Over 8,000 Subjects Receiving Abacavir in 34 Clinical Trials

A Cutrell, J Hernandez, M Edwards, J Fleming, W Powell, T Scott

GlaxoSmithKline, RTP, NC

Introduction

Hypersensitivity in the context of a reaction to abacavir (ABC) is a clinical syndrome characterized by the appearance of symptoms indicating multiorgan/body system involvement.¹ The mechanism of the ABC hypersensitivity reaction (HSR) has not been proven, and clinical risk factors have not been consistently identified. Such information would be of value to healthcare providers as an aid to making benefit/risk decisions when considering ABC as a component of ART for patients with HIV. A previous retrospective analysis was conducted on more than 5,000 ABC-treated subjects.² Using the collective data from 34 clinical trials, we continue that research effort with an updated retrospective analysis of risk factors for hypersensitivity reactions to abacavir.

Methods

Subjects Included for Study

- All protocols conducted by GlaxoSmithKline (GSK) involving at least 24 weeks of abacavir exposure with an authorized database by Q4, 2002 were included in this investigation.
- From the 34 protocols selected, only subjects exposed to ABC during the conduct of the study and with clinical risk factor data were included in this analysis. This comprises:
 - Subjects who began taking ABC in any combination on Day 1.
 - Subjects who were not randomized to ABC but subsequently received ABC during the conduct of the study.
 - *Does not include* subjects who received ABC during the follow-up phase of any study because complete clinical characteristics and hypersensitivity data were not available.

Identification of ABC HSR Cases

- Prior to 1999, cases of ABC HSR were identified using a broad clinical case definition that evolved as experience with the full spectrum of the syndrome accumulated.
- In 1999, GSK implemented a standard set of case report form (CRF) pages into all new protocols using ABC product(s).
 - Investigators were instructed to report suspected ABC HSR cases on the new CRF pages.
 - Cases of presumed HSR to ABC were more likely to be identified and reported by investigators.
 - In this clinical risk factor analysis, nine studies included the use of the ABC HSR CRF module.

Measurements and Evaluations

- Pertinent data fields from all clinical databases were aggregated into a single data repository:
 - Demographics
 - Baseline CDC Class
 - Baseline plasma HIV-1 RNA
 - Baseline CD4+ cell count
 - Antiretroviral treatment status (ART-naïve or ART-experienced at the time of ABC initiation)
 - Concurrent ART drugs (NNRTI, PI, d4T, 3TC + ZDV)
 - Year of ABC initiation
 - Presence or absence of ABC HSR CRF module
 - Geographic region (US, Europe, Latin America, or rest of world [ROW])
- All of these variables were available in each protocol and could be investigated as possible clinical risk factors for ABC HSR.
- Selected baseline laboratory test results and weight were also collected as potential clinical risk factors in protocols where available:
 - Bilirubin
 - Creatinine
 - AST (aspartate aminotransferase)
 - ALT (alanine aminotransferase)
 - Alkaline phosphatase
 - Baseline weight
- Laboratory values and weight were not collected in the ABC expanded access programs.
- For subjects exposed to ABC as a result of a treatment change during the course of a study, baseline measurements were defined as the last measurement prior to the initiation of ABC.

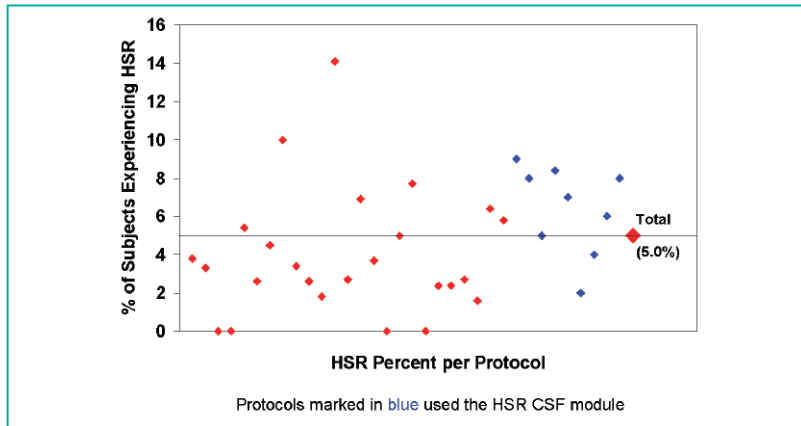
Data Analysis Methods

- Univariate logistic regression models were constructed to understand the individual predictive ability of each potential clinical risk factor.
- Two multivariable logistic regression models were fit to allow for the relationship between the outcome (HSR) to be described by a set of explanatory variables, rather than a single variable (as in univariate models). A stepwise selection procedure was used, although the use of the CRF module is automatically included in both models because it was an important design feature of later trials and had strong first-order predictive ability in the univariate model.
 - **Model 1** was designed to maximize the number of subjects that could be considered for the model.
 - **Model 2** was designed to maximize the number of factors that could be considered for the model.
- Subjects exposed to ABC during the conduct of the study without evidence of an ABC HSR served as the control group.

Results

- Among the 8038 subjects exposed to abacavir, 80% were male, 71% were ART-experienced. Global distribution was: 64% US, 22% Europe, 3% Latin America, 10% ROW.
- There were 403 (5.0%) cases of ABC HSR; 7635 subjects served as controls.
- HSR incidence ranged from 0 to 14%.

Figure 1 • Percentage of Subjects Experiencing ABC HSR Per Protocol



Univariate Models

Table 1 • Explanatory Variables Reaching Statistical Significance ($P < 0.10$)

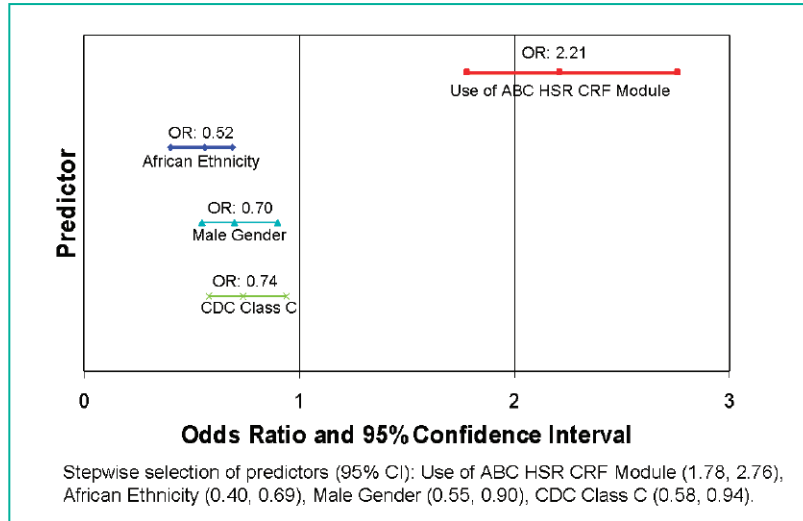
Most Prognostic Explanatory Variables	Odds Ratio	P value	% Reporting HSR (# HSR/N per subgroup)
African descent	0.68	0.004	4% (69/1852)
American Hispanic	1.27	0.09	6% (64/1053)
Male vs Female	0.76	0.02	5% (M; 305/6447) 6% (F; 98/1591)
CDC Class C vs CDC Class A + B	0.57	<0.0001	4% (Class C; 124/3459) 6% (not Class C; 279/4575)
Baseline CD4+ cell log count	1.25	0.01	4% (<200; 169/3973) 5% (200-350; 81/1592) 6% (>350; 149/2421)
Concurrent NNRTI use	0.76	0.02	4% (y; 106/2556) 5% (n; 297/5482)
Concurrent ZDV + 3TC use	0.82	0.07	4% (y; 129/2912) 5% (n; 274/5126)
Latin American geographic region	1.88	0.01	9% (18/203)
Year of ABC initiation	1.28	<0.0001	4% (1995; 2/50) 3% (1996; 3/120) 3% (1997; 68/2250) 4% (1998; 90/2079) 4% (1999; 30/807) 8% (2000; 95/1263) 8% (2001-2; 115/1469)
Use of ABC HSR CRF module	2.20	<0.0001	8% (y; 206/2670) 4% (n; 197/5368)

Note: None of the other potential risk factors reached statistical significance.

Multivariable Models

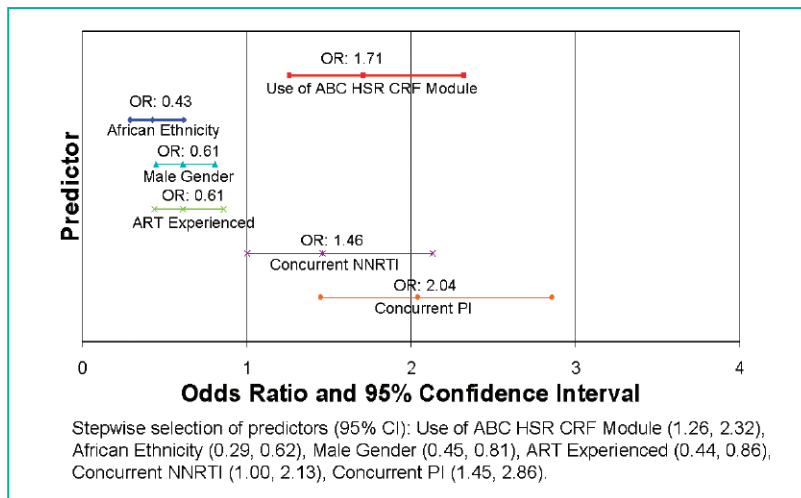
- Model 1:** Of the 8038 subjects, 7818 (including 389 HSR cases) have complete data for all of the potential risk factors when laboratory parameters and weight are not considered for inclusion. Figure 2 summarizes the results of the significant predictors in Model 1 including the ABC HSR CRF indicator as the required potential explanatory variable.

Figure 2 • Odds Ratio Estimates and 95% Confidence Intervals for Significant Predictors in Model 1 (N = 7818, P<0.05)



- **Model 2:** Of the 8038 subjects, 4222 (including 240 HSR cases) have complete data for the potential risk factors when laboratory parameters and weight are considered for inclusion. Figure 3 summarizes the results of the significant predictors for this expanded model.

Figure 3 • Odds Ratio Estimates and 95% Confidence Intervals for Significant Predictors in Model 2 (N = 4222, P<0.05)



Concurrent NNRTI use (NNRTI start not always recorded)

- ABC HSR was reported in 4% of 1006 subjects receiving concurrent **nevirapine (NVP)**, compared to 5% among the 7032 subjects without concurrent NVP.
- ABC HSR was reported in 5% of 1380 subjects receiving concurrent **efavirenz (EFV)**, compared to 5% among the 6658 subjects without concurrent EFV.

Discussion

- The strongest predictor for reporting an ABC HSR was the usage of the HSR CRF module.
- Subjects of African ethnicity (OR = 0.52), male gender (OR = 0.70) and CDC Class C or ART experience (OR = 0.74, 0.61, respectively) had lower odds of reporting ABC HSR.
- More than 1800 subjects concurrently initiated ABC and a PI, known to be associated with the development of rash.
- There was not consistent evidence that concurrent NNRTI or PI use increased the reporting of ABC HSR. However, there is potential for confusion in the diagnosis of a reaction to ABC when these agents are taken (and started) concurrently as seen in Model 2.
- Subjects with CDC Class C and/or ART experience may report fewer signs and symptoms thought to be associated with ABC HSR.

Conclusions

- ◆ The incidence of hypersensitivity in this largest investigation of ABC HSR clinical risk factors to date was 5.0%.
- ◆ Multivariable models identified African ethnicity, male gender, and baseline CDC Class C with a reduced risk.
- ◆ The most significant predictor for reporting HSR was the usage of the ABC HSR CRF module.
- ◆ No changes in the diagnosis and management of ABC HSR are recommended based on these results.

References

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2. Symonds W, Cutrell A, et al. Risk factor analysis of hypersensitivity reactions to abacavir. *Clin Ther.* 2002;24:565-573.

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