Letter to the Editor

Pharmacogenetics of abacavir hypersensitivity: A systematic review and meta-analysis of the association with HLA-B*57:01

To the Editor:

Hypersensitivity reactions to abacavir (a nucleoside analogue inhibitor of HIV reverse transcriptase) have been associated with HLA-B*57:01 allele carriage.[1] Although pharmacogenetic testing for HLA-B*57:01 before abacavir prescription has become routine practice, its value has been questioned after reports of low sensitivity in Hispanics and Africans.[2] Nevertheless, 2 large multiethnic studies found HLA-B*57:01 carriage to be strongly associated with abacavir hypersensitivity diagnosed by clinical criteria and patch testing in whites and blacks, suggesting that the apparent lower sensitivity of HLA-B*57:01 in populations with low prevalence of the allele was due to a higher rate of false positives.[3,4]

Much has been published on the association between HLA-B*57:01 carriage and abacavir-induced hypersensitivity, but a comprehensive quantitative synthesis of the evidence taking into account differences in ethnicity and diagnostic methods is lacking. We systematically assessed and quantitatively analyzed this association.

Four electronic databases (MEDLINE, Scopus, Embase, and Thomson Reuters Web of Science) were searched in April 2013, using the following query: "abacavir AND (hypersensitivit* OR allerg*) AND (HLA OR genetic*)". We also searched unpublished clinical trials in the US National Institute of Health trial database (ClinicalTrials.gov) and the GlaxoSmithKline Clinical Study Register. We included case-control studies with abacavir-tolerant controls (patients with a negative skin patch test result and/or no clinical symptoms of a hypersensitivity reaction in 6 or 12 weeks after exposure) evaluating the association between HLA-B*57:01 carriage and abacavir

TABLE I. Frequency of abacavir-hypersensitive cases and abacavir-tolerant controls and summary ORs

Reference	Population, n (% males; mean age)		Carriers of HLA-B*57:01 allele, n (%)		OR (95% CI)	Ethnic group
	Cases	Abacavir-tolerant controls	Cases	Controls		
Clinical: Broad criteria						
Mallal et al[5]	18 (89; 44.8)	167 (87; 42.8)	14 (78)	4 (2)	142.6 (32.2-632.5)	Whites (except for 20 controls)
Hetherington et al[6]	84 (93; 40.3*)	113 (91; 39.8*)	37 (44)	1 (1)	88.2 (11.8-661.5)	Multiethnic
Hughes et al[7]	13 (85; 34*)	51 (90; 37*)	6 (46)	5 (10)	7.9 (1.9-32.9)	Whites (except for 4 controls)
Stekler et al[10]	9 (†; 30.6)	41 (†; 33.5)	2 (22)	0 (0)	27.7 (1.2-635.6)	Multiethnic
Rodriguez-Novoa et al[11]	26 (†; 41*)	27 (†; 45*)	11 (42)	1 (4)	19.1 (2.2-162.6)	Hispanic
CNA30027, CNA30032, CNA30021, CNA30024, EPV40001 trials[15]	564 (77‡; 41.5‡)	725 (74‡; 40.3‡)	241§ (43)	12§ (2)	44.3 (24.5-80.3)	Multiethnic
Colombo et al[12]	108†||	175†||	35 (30)	3 (2)	24.2 (7.2-80.9)	Multiethnic
Mallal et al[3]	66†||	781†||	30 (46)	19 (2)	33.4 (17.2-65.0)	Multiethnic
Rauch et al[13]	131†||	140†||	41§ (31)	2 (1)	31.4 (7.4-133.2)	Multiethnic (mostly whites)
Saag et al[4]	198 (91; 44)	408 (82; 41)	67 (34)	10 (3)	20.4 (10.2-40.7)	Multiethnic
Munderi et al[14]	6†||	241†||	0 (0)	0 (0)	40.2 (2.2-721.1)	Black (sub-Saharan)
Total	1223	2869	484 (40)	57 (2)	32.1 (22.2-46.4)	
Clinical: Strict criteria						
Martin et al[8]	18 (83; 45.0)	230 (86; 42.6)	17 (94)	4 (2)	960.5 (101.6-9,077.1)	All cases and 196 (85%) controls were of European descent
CNA30027, CNA30032, CNA30021, CNA30024, EPV40001 trials[15]	245 (76‡; 41.5‡)	623 (81‡; 41.8‡)	122§ (50)	12§ (2)	50.5 (27.1-94.2)	Multiethnic
Colombo et al[12]	25†||	175†||	20 (80)	3 (2)	229.3 (51.0-1,032.3)	Multiethnic
Rauch et al[13]	27†||	140†||	21§ (78)	2 (1)	241.5 (45.7-1,276.3)	Multiethnic (mostly whites)
Total	315	1168	180 (57)	21 (2)	177.7 (48.4-652.0)	
Patch testing						
Phillips et al[9]	7†||	11†||	7 (100)	1 (9)	105.0 (3.7-2,948.1)	Not specified
Mallal et al[3]	23†||	819†||	23 (100)	25 (3)	1464.4 (86.5-24,783.6)	Multiethnic
Rauch et al[13]	4†||	140†||	4 (100)	2 (1)	498.6 (20.8-11,968.0)	Multiethnic (mostly whites)
Saag et al[4]	47 (91; 44)	408 (82; 41)	47 (100)	10 (3)	3605.5 (297.9-62,514.4)	Multiethnic
Total	81	1378	81 (100)	38 (3)	859.1 (189.2-3,901.4)	

*Value of median age presented. For Hetherington et al,[6] the values presented correspond to the 85 cases and 115 controls initially included.

†Sex not specified.

‡The values presented encompass "extra patients" for whom HLA-B*57:01 information was not obtained. Nevertheless, the number of these "extra patients" was never superior to 13.

§Estimated value obtained from the available data.

||Age not specified.

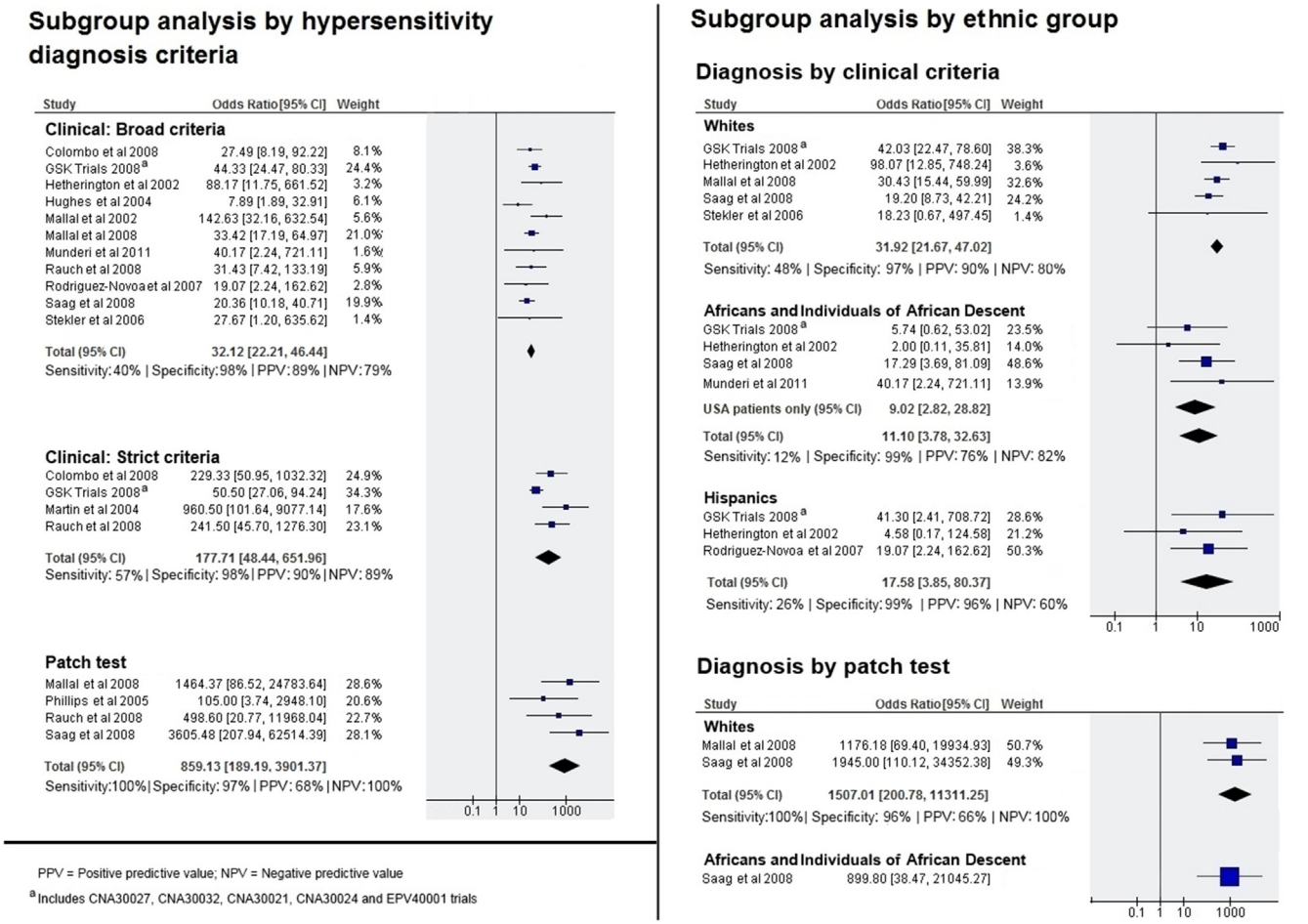

FIG 1. Association between HLA-B*57:01 expression and abacavir-induced hypersensitivity according to diagnostic criteria and ethnic group.

hypersensitivity. Whenever possible, information on participants' sex, age, and ethnicity was recorded. For each outcome, quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation working group approach (see reference E1 in this article's Online Repository at www.jacionline.org).

We calculated odds ratio (OR), sensitivity, specificity, and positive and negative predictive values using classical methods. For ORs, a continuity correction of 0.5 or 1.0 was applied when 1 or 2 cells had a 0 count, respectively. A random-effects meta-analysis with inverse variance weighting was used to estimate pooled OR and respective 95% CIs for the association between HLA-B*57:01 carriage and abacavir hypersensitivity. Heterogeneity was evaluated with I^2 and Cochran Q statistics. An I^2 value of more than 50% and a Cochran Q test P value of less than .100 were considered to represent substantial heterogeneity. Review Manager (RevMan) version 5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used for the meta-analysis and forest plots.

For the primary outcome, results were stratified according to hypersensitivity diagnosis criteria into broad (standard) clinical criteria, strict clinical criteria, and immunological criteria (abacavir patch testing; see reference E2 in this article's Online Repository at www.jacionline.org). Strict clinical criteria were considered when cases initially defined by broader clinical criteria were reassessed, or when additional clinical criteria were used to define a subgroup of cases. Results were further stratified by ethnicity (whites, blacks, and Hispanics). Differences between subgroups were also evaluated. P values of less than .05 were considered significant.

Twelve studies[3-14] and 1 trial register[15] (of 1195 publications and 65 trial registers found) met the inclusion criteria and were included in the meta-analysis (flowchart and funnel plot in Fig E1 of this article's Online Repository at www.jacionline.org). In total, 1234 cases and 2943 abacavir-tolerant controls were analyzed. Some cases were later reclassified after the application of stricter clinical criteria or the performance of patch tests. In brief, we compared 1223 cases defined by broad clinical criteria with 2869 controls, 315 cases defined by strict clinical criteria with 1168 controls,[8,12,13,15] and 81 cases with patch test confirmation with 1378 controls.[3,4,9,13] Information on participants' age, sex, and ethnic group (where available) is presented in Table I.

Abacavir hypersensitivity was diagnosed on the basis of only clinical criteria in 9 studies[5-8,10-12,14,15] and clinically and immunologically (at least in some participants) in 4 studies.[3,4,9,13]

All studies except 1, in which no participants carried the HLA-B*57:01 allele,[14] found a significant association between HLA-B*57:01 expression and abacavir hypersensitivity. The association was significant regardless of the diagnostic