

Table 1 (continued)

Outcome	Mean (SD)	F Value	P Value
No. of physician visits because of asthma in the past 12 months			
eNO, ppb			
≤25	0.33 (0.75)	0.65	.42
>25	0.74 (2.24)		
Obesity			
Obese BMI	0.73 (2.30)	1.22	.30
Overweight BMI	0.53 (1.16)		
Normal BMI	0.38 (1.30)		
eNO × obesity			
≤25 ppb × obese BMI	0.56 (1.03)	1.29	.28
≤25 ppb × overweight BMI	0.22 (0.60)		
≤25 ppb × normal BMI	0.17 (0.38)		
>25 ppb × obese BMI	0.89 (3.04)		
>25 ppb × overweight BMI	0.74 (1.38)		
>25 ppb × normal BMI	0.59 (1.80)		

Abbreviations: ED, emergency department; eNO, exhaled nitric oxide; ppb, parts per billion.

^aA violation of the assumption of equal variance for analysis of variance (ANOVA) was detected. A nonparametric 2-factor ANOVA on the ranks of the outcome measures was performed to account for the violation. The F test statistics and corresponding P values reported are based on the analysis using the ranks. However, raw means (SDs) of the outcomes are reported within eNO, within obesity, and within eNO × obesity groups. There was no statistically significant interaction of eNO and obesity for any asthma symptom 12-month EOT outcomes, indicating that the pattern of means across obesity groups were similar among the greater than 25 ppb and 25 ppb or less eNO groups. Likewise, there were no statistically significant differences in the means of the eNO groups or weight groups.

prevented the use of 111 of the patients in the analyses. Among those in the eNO and BMI sample, approximately 60% had current asthma (defined as a physician's diagnosis and asthma symptoms in the last 12 months), the remaining students had undiagnosed asthma (multiple asthma symptoms in the previous 12 months without a physician diagnosis), 71% were black, and 40% were male (mean [SD] age, 15.5 [1.0] years). The geometric mean eNO at 12-month EOT was 24.2 ppb (95% confidence interval, 21.5–27.2 ppb), with 53% having elevated eNO levels. The mean (SD) BMI was 27.4 (7.5), and the mean (SD) BMI percentage was 81.8% (20.9%), with nearly 40% of the sample being considered obese (eTable 1).

Elevated eNO levels were not related to any of the 4 asthma symptoms studied (Table 1). Similarly, obese, overweight, and normal weight categories were not related to any of the 4 asthma symptoms. However, there is a trend of increased symptoms for obese and overweight individuals compared with normal BMI participants, but this trend is not significant. The eNO × obesity interaction term directly examines the question of whether obese, overweight, or normal body status alters the association between eNO and asthma symptoms. None of these interaction terms are significant, suggesting that BMI does not alter the association between eNO and asthma symptoms.

We also examined the association between eNO and BMI category controlling for race or sex. The association between eNO and obesity was not significant overall ($P = .39$) or after controlling for race ($P = .34$) or sex ($P = .499$) (eTable 2). There was no significant association between eNO and obesity after stratification for race (black race $P = .15$, white/other race $P = .63$) or within sex (male $P = .70$, female $P = .34$).

This is the first study, to our knowledge, to examine the association of eNO to asthma symptoms by BMI category in a southern, rural, largely black, adolescent population. Other strengths of this study are a relatively large sample generally representative of high school students in rural Georgia. The participating adolescents represented a large variation of BMIs and socioeconomic backgrounds. Limitations of the study include reliance on self-reported height, weight, and asthma symptoms. Other limitations included randomly missing data, reducing the sample size, and limited geographic diversity. Although these results did not find a direct effect of BMI on eNO, our results suggest that when clinicians use eNO for assessing asthma in patients, consideration of BMI may not be required.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.09.431>.

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Raltegravir-induced drug reaction with eosinophilia and systemic symptoms syndrome in a child



Clinical syndromes of drug hypersensitivity have been reported in the literature for many decades; however, the more inclusive term of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome was first described in 1996 by Bocquet and colleagues¹ and is characterized by fever, severe rash, lymphadenopathy, hepatitis, and hematologic abnormalities.¹ Only recently have newer

medications known as integrase inhibitors been reported to cause DRESS syndrome in adults.^{2–5} The following is the first reported case, to our knowledge, of DRESS syndrome in a child caused by raltegravir.

A 10-year-old African American girl with well-controlled perinatally acquired human immunodeficiency virus (HIV) infection, presented with a pruritic, papular rash on her chest that spread diffusely and “dark eyes” for 10 days. Review of systems was notable for

Table 1
Cases of Raltegravir-Induced DRESS Syndrome

Age, y/Sex	Race	CD4, mm ³ /mL (%)	Viral Load, copies/mm ³	Presentation	Treatment	Outcome	Reference
10/F	Black	1,066 (40)	<40	1) Rash 2) Lymphadenopathy 3) Liver involvement 4) Eosinophilia	Discontinuation of raltegravir treatment Methylprednisolone	Full recovery Normal liver function in 6 weeks	PR
18/F	Hispanic	692 (35)	23	1) Fever 2) Rash 3) Lymphadenopathy 4) Pulmonary involvement 5) Liver involvement 6) Eosinophilia	Discontinuation of raltegravir treatment Hydroxyzine Prednisone	Full recovery Relapse attributable to nonadherence requiring reinitiation of prednisone	4
64/F	Black	522 (Unknown)	Undetectable	1) Rash 2) Lymphadenopathy 3) Liver involvement 4) Leukocytosis 5) Eosinophilia 6) Hypertension	Discontinuation of raltegravir treatment Methylprednisolone Diphenhydramine Amlodipine	Full recovery Normal liver function in several days	5
46/F	Black	412 (28)	<40	1) Fever 2) Rash 3) Lymphadenopathy 4) Liver involvement 5) Kidney involvement	Discontinuation of raltegravir treatment	Full recovery Normal liver function in 2 months	2
55/F	Black	305 (19)	Unknown	1) Fever 2) Rash 3) Liver involvement 4) Eosinophilia	Discontinuation of raltegravir treatment Prednisolone	Full recovery Normal liver function in 6 weeks	3

Abbreviation: PR, present report.

malaise, epistaxis, dark urine, and subjective fever with cough a few days before onset of the rash. One month earlier, she was switched from zidovudine, lamivudine, and lopinavir-ritonavir therapy to abacavir, emtricitabine, and raltegravir for neutropenia and leukopenia thought to be secondary to zidovudine. HLA B-5701 test results were negative. She denied taking other medications or supplements.

In the emergency department, she was afebrile with normal vital signs. Her examination findings were notable for scleral icterus, jaundice, and hepatomegaly without splenomegaly. She had a diffuse, fine, erythematous maculopapular rash across the face, chest, back, and extremities with excoriations but no mucosal involvement. She had axillary and inguinal lymphadenopathy.

Laboratory test results were significant for the following: aspartate aminotransferase, 3,918 U/L; alanine aminotransferase, 2809 U/L; γ -glutamyltransferase, 235 U/L; ammonia, 122 μ g/dL; total bilirubin, 11.5 mg/dL; and direct bilirubin, 8.27 mg/dL. The white blood cell count was 9,580 cells/ μ L with an eosinophil count of 1,740 cells/ μ L (18.2%). She was admitted to the intensive care unit. Her liver dysfunction peaked at a prothrombin time of 33.4 seconds, international normalized ratio of 3.06, and partial thromboplastin time of 51.9 seconds, with factor 5 activity of 50.6% (reference range, 65%–140%) and factor 7 activity of 13.2% (reference range, 60%–130%). Abdominal ultrasonography revealed a normal appearance of the liver. The results of chest radiography were normal. HIV RNA quantification was less than 40 copies/mL, and the CD4 level was 1,066 mm³/mL.

All antiretroviral therapy was held, and her mental status remained stable. The results of a workup for other causes of acute liver failure were negative, including negative IgM serologic test results for cytomegalovirus, Epstein-Barr virus, measles, human herpes virus (HHV) 6, and hepatitis A, B, and C. Ceruloplasmin and alkaline phosphatase levels were normal. The test results for autoimmune antibodies, including antineutrophil cytoplasmic antibody, anti-double-stranded DNA, anti-liver kidney microsomal type 1, and anti-smooth muscle antibody, were negative;

however, the antinuclear antibody titer was 1:160 with normal C3 and C4 levels and an IgG level elevated to 2,054 mg/dL. The results of pharyngeal swabbing for group A Streptococcus and respiratory viral polymerase chain reaction panel were negative.

Intravenous methylprednisolone was administered on admission at a dose of 2 mg/kg daily divided every 6 hours on days 1 to 2, followed by 1 mg/kg daily divided every 12 hours on days 3 to 4, and then 0.5 mg/kg daily on day 5. She was then transitioned to oral prednisolone at a dose of 0.625 mg/kg daily followed by a prolonged taper over 8 weeks. On discharge (hospital day 7), the rash had resolved, liver function had improved, and the coagulation panel had normalized. Her liver function normalized after 6 weeks of prednisone, and the results of a liver biopsy performed after completion of corticosteroid therapy was normal. Upon her recovery, she underwent patch testing for possible abacavir hypersensitivity. Patch testing was performed using 1%, 10%, and 25% concentrations of abacavir. Results were read at 48 and 96 hours and were negative.

The pathophysiologic mechanisms of DRESS syndrome are not well understood, with several proposed mechanisms, including reactivation of viral infections, genetic predisposition leading to immune imbalance, and defects in detoxification of the causative drug, which results in reactive metabolites.¹ The standard management consists of antihistamines and discontinuation of use of the offending agent.¹ The use of corticosteroids remains controversial, but corticosteroids are often considered in cases with extensive skin, pulmonary, and hepatic involvement.^{2–5}

Currently, there are 2 diagnostic systems developed by the European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biologic Samples (RegiSCAR) program and Japanese consensus group in an effort to standardize the diagnosis of DRESS syndrome and to distinguish the various drug reactions from one another.¹ The RegiSCAR scoring system also surveys other cutaneous reactions, such as Stevens-Johnson syndrome.

The system classifies cases as no case, possible case, probable case, and definite case based on the number of criteria met, with a score of greater than 5 considered definite. Criteria include (1) temperature higher than 38°C, (2) lymphadenopathy, (3) skin involvement, (4) involvement of at least one organ system, (5) atypical lymphocytes, (6) eosinophilia, (7) time of resolution of 15 days or longer, and (8) exclusion of other causes, with hepatitis serologic findings, antinuclear antibody, and blood cultures.¹ The Japanese consensus group describes a scoring system that includes similar criteria but also expands to include leukocytosis and HHV 6 reactivation.⁶ Our patient met the criteria for definite DRESS syndrome with a RegiSCAR score of 6 and a Japanese consensus group score of 6 after appropriate evaluation for other etiologies.⁶

DRESS syndrome has been well documented in the literature in adults with HIV on various antiretroviral regimens; however, it is rarely described in children. Integrase inhibitors, such as raltegravir, are a newer class of oral HIV-1 medications that have a long safety record with relatively few adverse effects.⁷ A MEDLINE search using the Medical Subject Headings of *DRESS syndrome* and *raltegravir* yielded 4 reported cases of raltegravir-induced DRESS syndrome, all in adult patients with an age range of 18 to 64 years (Table 1).^{2–5} All patients were female, 3 were of African descent, and all presented with fever, morbilliform rash, elevated transaminases, and lymphadenopathy. Three had probable and 1 had definite DRESS syndrome based on the RegiSCAR scoring. The patients did well, and only 1 patient relapsed with DRESS syndrome.⁴

Although abacavir hypersensitivity is a common cause of drug rash and eosinophilia in HIV, this was not the case in our patient because she had 2 negative test results that correlate with cutaneous reactions to abacavir, patch testing at multiple concentrations, and HLA B-5701 testing.^{8–10} Patch testing to abacavir is an accurate way to diagnose abacavir sensitivity. This correlates with HLA B-5701 testing in patients with HIV and suspected hypersensitivity reactions to abacavir with positive and negative predictive values of 82% and 85%, respectively. The HLA B-5701 test specificity is 90% to 100%, regardless of presentation.^{8–11} There are no published cases of DRESS syndrome associated with emtricitabine, and our patient had history of long-term lamivudine use (a similar nucleoside analogue) before starting emtricitabine therapy. This evidence strongly suggests that the culprit drug in our case was raltegravir.

DRESS syndrome is an uncommon hypersensitivity reaction that, when seen in children, is typically associated with anticonvulsant or antibiotic therapy. Raltegravir has been infrequently associated with DRESS syndrome. As with other antiretroviral medications, practitioners should closely monitor patients when switching to this class of therapeutic agents for serious drug reactions.

Acknowledgments

We thank Dr Kenneth Boyer for his input. Dr Logan acknowledges funding from the National Institutes of Health under grant K08AI112506.

Contact urticaria caused by alcohol Clinical characteristics and cross-reactions

Contact urticaria (CU) from alcohol is often underdiagnosed and undertreated because it is much less frequent than allergic eczema and is transient in nature.¹ Its mechanism can be mediated by immunologic and nonimmunologic processes.² Few data on CU caused by alcohol have been published. This study investigated

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clinical characteristics, cross-reactions, and association with alcohol consumption in patients who had CU caused by ethanol (ethyl alcohol).

Patients who had an urticarial reaction occurring on the skin within 30 minutes after direct contact with ethanol and who attended Siriraj Hospital during a 3-year period were enrolled. Demographic data, symptoms after application of cosmetic