JAMA Dermatology | Original Investigation

Association of *APOA5* and *APOC3* Genetic Polymorphisms With Severity of Hypertriglyceridemia in Patients With Cutaneous T-Cell Lymphoma Treated With Bexarotene

Irene Cabello, MD; Pedro Alia, MD, PhD; Xavier Pintó, MD, PhD; Cristina Muniesa, MD; Ricardo Fernandez-de-Misa, MD; Yerai Peñate, MD; Mercedes Morillo, MD; Amparo Perez-Farriols, MD; Teresa Estrach, MD, PhD; Rosa Izu, MD, PhD; Fernando Gallardo, MD; Concepción Román, MD; Iván Cervigón, MD; Ariadna Ortiz-Brugues, MD; Pablo L. Ortiz-Romero, MD, PhD; Octavio Servitje, MD, PhD

IMPORTANCE Hypertriglyceridemia is the most frequent and limiting adverse effect of bexarotene therapy in cutaneous T-cell lymphoma (CTCL). Despite standard prophylactic measures, there is a wide variability in the severity of this complication, which could be associated with both genetic and environmental factors.

OBJECTIVES To analyze the association between genetic polymorphisms of apolipoprotein genes *APOA5*, *APOC3*, and *APOE* and the severity of hypertriglyceridemia during bexarotene therapy and to optimize patient selection for bexarotene therapy based on adverse effect profile.

DESIGN, SETTING, AND PARTICIPANTS This case series study was conducted in 12 university referral hospitals in Spain from September 17, 2014, to February 6, 2015. One hundred twenty-five patients with a confirmed diagnosis of CTCL who had received bexarotene therapy for at least 3 months were enrolled. Nine patients were excluded owing to missing analytic triglyceride level data, leaving a study group of 116 patients. Data on demographic and cardiovascular risk factor were collected, and a complete blood analysis, including lipid profile and genetic analysis from a saliva sample, was performed.

MAIN OUTCOMES AND MEASURES Primary outcomes were the maximal triglyceride levels reported in association with the minor alleles of the polymorphisms studied.

RESULTS Among 116 patients, the mean (SD) age was 61.2 (14.7) years, 69 (59.5%) were men, and 85 (73.2%) had mycosis fungoides, the most prevalent form of CTCL. During bexarotene therapy, 96 patients (82.7%) experienced hypertriglyceridemia, which was severe or extreme in 8 of these patients (8.3%). Patients who carried minor alleles of the polymorphisms did not show significant differences in baseline triglyceride concentrations. After bexarotene treatment, carriers of at least 1 of the 2 minor alleles of *APOA5* c.-1131T>C and *APOC3* c.*40C>G showed lower levels of triglycerides than noncarriers (mean [SD], 241.59 [169.91] vs 330.97 [169.03] mg/dL, respectively; $P = .02$).

CONCLUSIONS AND RELEVANCE These results indicate that the screening of *APOA5* and *APOC3* genotypes may be useful to estimate changes in triglyceride concentrations during bexarotene treatment in patients with CTCL and also to identify the best candidates for bexarotene therapy based on the expected adverse effect profile.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Octavio Servitje, MD, PhD, Dermatology Department. Hospital Universitari de Bellvitge. IDIBELL, c/Feixa Larga s/n 08907, L'Hospitalet de Llobregat, Barcelona, Spain (oservitje@bellvitgehospital.cat).

JAMA Dermatol. 2018;154(12):1424-1431. doi:10.1001/jamadermatol.2018.3679
Published online October 24, 2018.

Bexarotene, a synthetic retinoid and member of a subclass of retinoids called *rexinoids,*[1] was approved by the US Food and Drug Administration for the treatment of cutaneous T-cell lymphoma (CTCL) in 1999 and licensed in 2002 in Europe for the treatment of patients with advanced CTCL (stages IIB-IVB) refractory to at least 1 systemic treatment. Bexarotene has also been shown to be an effective and safe treatment for refractory early-stage CTCL (stages I-IIA).[1-4]

Dyslipidemia, mainly hypertriglyceridemia, and central hypothyroidism are the most common adverse effects of bexarotene. These effects are dose-related and reversible when drug treatment is discontinued.[5-7] This bexarotene-induced hypertriglyceridemia may be severe, and triglyceride levels of 991.15 mg/dL or greater (reference threshold, <160 mg/dL; to convert to millimoles per liter, multiply by 0.0113) can increase the risk of pancreatitis.[8] Guidelines recommend the use of prophylactic hypolipemic therapy from 1 week before beginning bexarotene treatment to maintain triglyceride levels less than 486.73 mg/dL in the general population and less than 309.73 mg/dL in patients with known cardiovascular disease.[1] It is recommended to start that treatment with a fibrate, usually fenofibrate, and simultaneously or later add a statin or ω-3 fatty acids if there is poor control of the dyslipemia.[1,7,9]

Despite these prophylactic measures and strict lifestyle control, hypertriglyceridemia often cannot be avoided, and it is the principal cause of bexarotene therapy discontinuation. Risk factors for development of severe hypertriglyceridemia after bexarotene treatment have not been well defined. Environmental and genetic factors are both known to alter plasma triglyceride levels in the general population.[10] Triglyceride levels vary widely among and within individuals during bexarotene treatment. Thus, it would be of interest to identify genetic factors associated with the risk of developing severe hypertriglyceridemia during bexarotene therapy. In the general population, genes that code for apolipoprotein A5 (ApoA5), ApoC3, and ApoE are consistently directly associated with triglyceride concentrations. The minor allele of the *APOA5* c.-1131T>C and c.56G>C single-nucleotide polymorphism, the *APOC3* c.*40C>G polymorphism, and the *APOE* c.388T>C and c.526C>T polymorphisms are associated with higher triglyceride levels and also with risk for coronary artery disease, metabolic syndrome, and stroke.[11-15]

The aim of this study was to analyze the association of these genetic polymorphisms of *APOA5* (OMIM 606368), *APOC3* (OMIM 107720), and *APOE* (OMIM 107741) with the severity of bexarotene-associated hypertriglyceridemia in patients with CTCL.

Key Points

Question Do *APOA5*, *APOC3*, and *APOE* polymorphisms play a role in the severity of hypertriglyceridemia in patients receiving bexarotene therapy for cutaneous T-cell lymphoma?

Findings In this case series study of 116 patients with cutaneous T-cell lymphoma who underwent at least 3 months of bexarotene treatment, those who carried the minor alleles of *APOA5* c.-1131T>C or *APOC3* c.*40C>G experienced less severe hypertriglyceridemia.

Meaning Screening for *APOA5* and *APOC3* polymorphisms may help physicians who treat patients with cutaneous T-cell lymphoma identify the best candidates for bexarotene treatment.

Methods

This retrospective, observational, noninterventionist, multicenter case series study was conducted in 12 Spanish university hospital dermatology departments from September 17, 2014, to February 6, 2015. The study was approved by the Clinical Research Ethics Committee of Bellvitge University Hospital, Barcelona, Spain, as the reference center and thereafter from the medical ethics committees of the remaining hospitals (Hospital Universitari de Bellvitge, Barcelona; Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife; Complejo Hospitalario Universitario Insular Materno-Infantil, Las Palmas de Gran Canaria; Hospital Universitario Virgen del Rocio, Sevilla; Hospital General Universitario de Valencia, Valencia; Hospital Clínic de Barcelona, Barcelona; Hospital Universitario de Basurto, Bilbao; Hospital del Mar, Barcelona; Hospital Universitario de Salamanca, Salamanca; Hospital Nuestra Señora del Prado, Talavera; Hospital Arnau de Vilanova, Lleida; and Hospital Universitario 12 de Octubre, Madrid). Participants provided written informed consent according to the Declaration of Helsinki[16] protocols.

Study Design and Data Collection

Patients eligible for inclusion were 18 years or older, had a confirmed diagnosis of CTCL, and had been treated for at least 3 months with bexarotene. To prevent selection bias, the investigator at each center obtained the list of living patients with CTCL and ordered them in reverse order of date of diagnosis, starting from the patient with the most recent diagnosis. Patients with severe renal or hepatic failure or who were being treated with drugs with a known hypertriglyceridemic adverse effect were excluded. Participants were interviewed to collect information on demographic characteristics, cardiovascular risk factors, and lifestyle habits. The following clinical findings were recorded: age, sex, weight, height, and body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), smoking and alcohol consumption, diabetes, hypertension, previous dyslipidemia, physical exercise and dietary habits, histologic subtype, initial CTCL stage at diagnosis and stage at the beginning of bexarotene treatment, duration of bexarotene treatment, and response to the drug.

For the evaluation of clinical response to bexarotene, all participating centers uniformly used the standard end points proposed by Olsen et al.[17] A saliva sample was collected during the medical visit for genetic study. Baseline analytic data, including renal and liver function, lipid profile, complete blood cell count, and thyroid hormone levels at 1 and 3 months after initiation of bexarotene treatment, were collected retrospectively. All pharmacologic treatment of these patients was provided as part of usual clinical practice.[18] Standard recommendations for bexarotene use in CTCL established that patients should start at a low dose and subsequently increase it

Table 1. Clinical and Demographic Information of 116 Patients With CTCL

Characteristic	No. (%)
Age, mean (SD) y	61.2 (14.7)
Male sex	69 (59.5)
BMI, mean (SD)	26.9 (4.5)
Cigarette smoker	32 (28.8)
Alcohol drinker	30 (27.0)
Diabetes	18 (15.5)
Hypertension	26 (22.4)
CTCL clinical form	
Classic mycosis fungoides	85 (73.2)
Folliculotropic mycosis fungoides	22 (19.0)
Sézary syndrome	9 (7.8)
CTCL stage at diagnosis	
I	69 (59.5)
IIA/IIB	4 (3.4)/22 (18.9)
III	14 (12.1)
IVA/IVB	6 (5.2)/1 (0.9)
CTCL stage at start of bexarotene treatment	
I	36 (31.0)
IIA/IIB	17 (14.7)/17 (14.7)
III	24 (20.6)
IVA/IVB	18 (15.6)/4 (3.4)
Bexarotene response	
Partial response	61 (52.9)
Complete response	37 (31.9)
Stable disease	15 (12.9)
Disease progression	3 (2.6)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CTCL, cutaneous T-cell lymphoma.

up to the maximum recommended dose of 300 mg/m^2/d based on the patient's tolerance and the level of hypertriglyceridemia. In our study, these recommendations were uniformly adopted in every participating center. Thus, all patients were treated with bexarotene at an initial dose of 150 mg/m^2/d, which was subsequently titrated to full doses of 300 mg/m^2/d after 1 to 3 months of therapy depending on tolerance.[1,6,7] They also had received prophylactic hypolipidemic therapy from 1 week before the beginning of bexarotene treatment and 50 µg/d of levothyroxine sodium from the beginning of treatment, both continuing throughout bexarotene treatment. The investigator at each center collected the clinical and analytic data and thereafter provided those to a contract research organization specifically designed for the study. All data were encrypted and rendered anonymous so that the information collected in the centralized database could not identify the patients in the study. The entire procedure was strictly accomplished with the requirements of confidentiality pursuant to Spain's Organic Law 15/1999 on Protection of Personal Data.

Genetic Studies

Gene variant analysis was performed in the clinical laboratory of Bellvitge University Hospital. Saliva samples were collected, preserved, and transported in saliva-collection tubes (Oragene; DNA Genotek). DNA was extracted from saliva in an automated system (Maxwell16, model MX3031; Promega Corporation). All samples were codified and anonymized, and only the investigators responsible for the laboratory had access to them.

We studied the presence of the minor allele vs homozygosis for the major allele for the following gene variants: c.-1131T>C (rs662799, *APOA5*); c.56G>C (rs3135506, *APOA5*); c.*40C>G (rs5128, *APOC3*); c.388T>C (rs429358, *APOE*E4*); c.526C>T (rs7412, *APOE*E2*). All were genotyped using allele-specific TaqMan probes (Life Technologies) in a real-time polymerase chain reaction system (iQ5; BioRad).

Statistical Analysis

All statistical analyses were performed using SPSS, version 19 statistical software (SPSS Inc). Deviations from Hardy-Weinberg equilibrium were assessed using the χ^2 test. Categorical and ordinal variables are presented as frequencies and percentages; means and SDs are used for continuous variables. The qualitative variables were analyzed using the χ^2 or Fisher exact test and the quantitative variables using the paired, 2-tailed *t* test. To analyze the lipid profile data, the maximal lipid value for the individual patient during follow-up was registered. Continuous variables that were not normally distributed were log transformed to achieve normal distribution before fitting statistical models. To analyze which variables were associated with maximal triglyceride concentrations during bexarotene therapy, we used a stepwise multiple linear regression model with the variable log-maximal triglyceride level as the dependent variable and log-baseline triglyceride level, age, sex, BMI, and presence of minor alleles of each polymorphism as risk factors. Statistical significance was set at 2-sided $P < .05$.

Results

One hundred twenty-five patients met the inclusion criteria. Nine were subsequently excluded because they had missing analytic triglyceride level data. Therefore, 116 patients constituted the study group. **Table 1** summarizes participants' baseline and disease characteristics. Mean age ranged from 34 to 88 years, and there was a male prevalence (69 [59.5%]). Mean (SD) BMI was 26.9 (4.5), and 18 of the 116 patients (15.5%) were obese (BMI >30). In our series, classic mycosis fungoides was the most prevalent form of CTCL, with 85 patients (73.2%) having this diagnosis. We found a predominance of advanced-stage disease (IIB-IVB) (63 patients [54.3%]) at the time of bexarotene treatment. After bexarotene treatment, 37 (31.9%) showed complete response, 61 (52.6%) had partial response, 15 (12.9%) remained with stable disease, and 3 (2.6%) had lymphoma progression. Thus, the overall response rate (complete response + partial response) was 84.5% and the overall control rate (complete response + partial response + stable disease) was 97.4%. Patients were treated with bexarotene for a mean of 33 months (range, 3-140 months). As bexarotene therapy was discontinued, we observed clinical progression of the disease in 19 patients (16.4%).

Blood Lipid Analysis

Before bexarotene treatment, 83 of the 116 patients (71.5%) had normal triglyceride levels. Following the accepted recommendations, 112 patients (96.6%) initiated hypolipidemic therapy before bexarotene, with 99 (85.3%) receiving fibrates as the initial prophylactic lipid-lowering treatment. During bexarotene treatment, 96 patients (82.7%) developed hypertriglyceridemia. According to the Adult Treatment Panel III guidelines,[18] the hypertriglyceridemia was classified as borderline (150.44-194.69 mg/dL) in 12 patients (12.9%), high (194.69-495.58 mg/dL) in 53 (55.2%), very high (>495.58 mg/dL) in 23 (23.9%), and severe or extreme (≥991.15 mg/dL) in 8 (8.3%).

We observed statistically significant reductions in mean (SD) levels before and 2 analytic data points after bexarotene treatment in levels of thyrotropin (3.6 [15.1], 1.0 [2.6], and 1.9 [10.1] mIU/L; $P = .02$), free thyroxine (1.36 [1.72], 0.98 [0.99], and 1.04 [0.99] ng/dl; $P < .001$), leukocytes (7000 [2800], 6100 [2300], and 6100 [3000] cells/μL; $P = .01$), and high-density lipoprotein cholesterol (54.05 [19.31], 34.75 [19.31], and 0.9 [19.31] mg/dL; $P < .001$) and a significant increase in levels of creatinine (0.89 [0.24], 0.95 [0.27)], and 0.95 [0.27] mg/dL; $P = .009$); platelets (248.2 [68.1], 272.12 [75.9], and 271.9 [84.5] × 10^3/L; $P = .02$); total cholesterol (204.63 [40.54]; 250.97 [57.92], and 243.24 [65.64]; $P < .001$); and low-density lipoprotein cholesterol (123.55 [34.75], 158.30 [54.05], and 142.86 [57.92]; $P < .001$). (To convert the level of free thyroxine to picomoles per liter, multiply by 12.871; leukocytes to cells ×10^9/L, multiply by 0.001; high-density and low-density lipoprotein and total cholesterol to millimoles per liter, multiply by 0.0259; creatinine to micromoles per liter, multiply by 88.4; and platelets to cells ×10^9/L, multiply by 1.0.) There were no statistically significant differences in glucose, liver profile, or hematocrit levels.

Genetic Studies

Genetic polymorphism frequencies and baseline characteristics are described in **Table 2**. The genotype distribution was in Hardy-Weinberg equilibrium. By dividing number of minor alleles by number of total alleles and multiplying the quotient by 100, we obtained similar allelic frequencies of the minor allele in each gene, ranging from *APOA5* c.-1131T>C as the most prevalent (9.5%) to the *APOA5* c.56G>C as the least prevalent (6.9%). These frequencies did not deviate from previous data of the general white population, according to the Exome Aggregation Consortium database, version 1.0.[19] We observed a significant difference in genotype frequency between men and women in the *APOA5* c.-1131T>C polymorphism (65.3% men vs 34.7% women among TT carriers vs 33.3% men vs 66.7% women among TC+CC carriers; $P = .007$) and in age in the *APOA5* c.56G>C polymorphism (62.6 vs 51.2 years among TT carriers vs TC+CC carriers; $P = .004$) and *APOE* c.526C>T polymorphism (59.8 vs 68.1 years; $P = .02$). Mean (SD) BMI was higher in carriers of *APOE* c.388 TT than in TC+CC carriers (27.3 [4.5] vs 24.9 [4.1]; $P = .04$). There were no significant genotype-related differences in any other baseline characteristics studied. Minor allele carriers showed lower total cholesterol values after bexarotene treatment for variants *APOA5* c.-1131T>C, *APOC3* c.*40C>G, and *APOE* c.526C>T, achieving statistical significance in the *APOA5* c.-1131T>C genotype (204.25 [42.47] mg/dL in TT carriers before treatment vs 203.09 [35.91] mg/dL in TC+CC carriers before treatment and 277.99 [42.86] mg/dL in TT carriers after treatment vs 248.65 [54.44] mg/dL in TC+CC carriers after treatment; $P = .046$). Triglyceride concentrations before and after bexarotene administration in each genetic polymorphism are shown in **Table 3**. At baseline, the minor allele carriers of all the genes except *APOA5* c.56G>C exhibited nonsignificantly higher plasma triglyceride concentrations than noncarriers. After bexarotene therapy, lower maximal triglyceride concentrations were seen when the minor allele was present. After adjusting for the baseline triglyceride level in every patient, for sex in *APOA5* c.-1131T>C, and for age in *APOA5* c.56C>G and *APOE* c.526C>T, the association between triglyceride level changes and these polymorphisms was not statistically significant. However, we grouped *APOA5* c.-1131T>C (carriers vs noncarriers, mean 1 [SD] adjusted maximal triglyceride level, 246.90 [172.57] vs 327.43 [169.91] mg/dL; $P = .10$) and *APOC3* c.*40C>G (carriers vs noncarriers, mean 1 [SD] adjusted maximal triglyceride level, 251.33 [172.57] vs 324.78 [171.68] mg/dL; $P = .14$) in a single variable, defining those patients carrying at least 1 of the minor alleles as carriers, and this association was significant for triglyceride reduction for carriers vs noncarriers (mean [SD] adjusted maximal triglyceride level, 241.59 [169.91] vs 330.97 [169.03] mg/dL; $P = .02$).

We observed a significant association between the initial triglyceride levels and their maximum increase during bexarotene treatment. For that, we performed an explanatory regression model of the log-maximal triglyceride, which showed that the only significant statistic variable was log-baseline triglyceride, accounting for 25% of the total variability (regression coefficient, 0.76 [95% CI, 0.51-1.01]; $R^2 = 0.253$; $P < .001$). The higher the baseline triglyceride concentration, the higher the maximal triglyceride concentration reached during bexarotene treatment.

Discussion

Cutaneous T-cell lymphoma is a rare disease with a small prevalence. Bexarotene is an effective systemic therapy for patients with advanced or refractory CTCL, but hypertriglyceridemia, which was recorded in 82.7% of our study patients, used to be a limiting adverse effect. In this study, we aimed to evaluate the influence of several *APO* gene polymorphisms in the severity of hypertriglyceridemia induced by bexarotene therapy in patients with CTCL. The purpose of screening was to identify ideal patient selection for bexarotene therapy based on the adverse effect profile, not to identify those who will respond from a therapeutic standpoint.

To our knowledge, this is the largest multicenter study[4,20,21] to date evaluating patients with treated with bexarotene and the first focusing on triglyceride metabolism. Our results showed that, according to what has been observed in the general population,[11-15] patients with CTCL who carry the minor allele of *APOA5* c.-1131T>C, c.56G>C, *APOC3*

Table 2. Genetic Polymorphism Frequencies and Baseline Characteristics of 116 Patients With CTCL

Characteristic by Genetic Polymorphism	Genotype		*P* Value
***APOA5* c.-1131T>C**	**TT**	**TC + CC**	
Patients, No. (%)	95 (81.9)	20 + 1 (18.1)	
Age, mean (SD), y	61.1 (14.9)	61.3 (13.8)	.95
Men, No. (%)	62/33 (65.3/34.7)	7/14 (33.3/66.7)	.007
Smoker, No. (%)	27 (29.3)	5 (26.3)	.79
BMI, mean (SD)	26.7 (4.2)	27.3 (5.8)	.61
TC level before treatment, mean (SD), mg/dL	204.25 (42.47)	203.09 (35.91)	.93
TC level after treatment, mean (SD), mg/dL	277.99 (42.86)	248.65 (54.44)	.046
TG level before treatment, mean (SD), mg/dL	138.94 (86.73)	149.56 (97.35)	.61
***APOA5* c.56G>C**	**GG**	**GC + CC**	
Patients, No. (%)	101 (87.1)	14 + 1 (12.9)	
Age, mean (SD), y	62.6 (14.5)	51.2 (12.2)	.004
Men, No. (%)	60 (59.4)	9 (60.0)	.97
Smoker, No. (%)	28 (28.6)	4 (30.8)	>.99
BMI, mean (SD)	26.6 (4.5)	28.5 (4.2)	.14
TC level before treatment, mean (SD), mg/dL	205.02 (43.24)	198.07 (27.03)	.55
TC level after treatment, mean (SD), mg/dL	273.36 (61.39)	272.59 (68.73)	.96
TG level before treatment, mean (SD), mg/dL	143.36 (92.92)	120.35 (50.44)	.34
***APOC3* c.*40C>G**	**CC**	**CG + GG**	
Patients, No. (%)	98 (84.5)	16 + 2 (15.5)	
Age, mean (SD), y	61.9 (14.7)	57.3 (14.4)	.22
Men, No. (%)	59 (60.2)	10 (55.6)	.71
Smoker, No. (%)	27 (28.1)	5 (33.3)	.76
BMI, mean (SD)	27.0 (4.7)	25.9 (3.1)	.34
TC level before treatment, mean (SD), mg/dL	203.86 (42.08)	206.95 (39.00)	.78
TC level after treatment, mean (SD), mg/dL	275.68 (63.32)	259.46 (57.53)	.32
TG level before treatment, mean (SD), mg/dL	134.51 (85.84)	174.34 (100.00)	.08
***APOE* c.388T>C**	**TT**	**TC + CC**	
Patients, No. (%)	96 (82.8)	19 + 1 (17.2)	
Age, mean (SD), y	61.9 (14.8)	57.6 (13.7)	.24
Men, No. (%)	58 (60.4)	11 (55.0)	.65
Smoker, No. (%)	26 (28.0)	6 (33.3)	.65
BMI, mean (SD)	27.3 (4.5)	24.9 (4.1)	.04
TC level before treatment, mean (SD), mg/dL	202.70 (38.61)	211.20 (53.67)	.41
TC level after treatment, mean (SD), mg/dL	271.43 (61.39)	281.85 (67.95)	.49
TG level before treatment, mean (SD), mg/dL	137.17 (83.19)	155.75 (112.39)	.42
***APOE* c.526C>T**	**CC**	**CT + TT**	
Patients, No. (%)	97 (83.6)	17 + 2 (16.4)	
Age, mean (SD), y	59.8 (14.6)	68.1 (12.9)	.02
Men, No. (%)	58 (59.8)	11 (57.9)	.88
Smoker, No. (%)	27 (29.3)	5 (26.3)	.79
BMI, mean (SD)	26.9 (4.7)	26.3 (3.6)	.56
TC level before treatment, mean (SD), mg/dL	206.18 (40.54)	194.59 (45.95)	.28
TC level after treatment, mean (SD), mg/dL	275.68 (62.55)	260.23 (62.16)	.33
TG level before treatment, mean (SD), mg/dL	140.71 (85.84)	143.36 (105.31)	.91

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); TC, total cholesterol; TG, triglycerides.

SI conversion factors: To convert TC to millimoles per liter, multiply by 0.0259; TG to millimoles per liter, multiply by 0.0113.

c.*40C>G, and *APOE* c.388T>C and c.526C>T polymorphisms had nonsignificantly higher baseline triglyceride levels. However, after bexarotene treatment was introduced, we observed that carriers of at least 1 of the minor alleles of *APOA5* c.-1131T>C and *APOC3* c.*40C>G showed a significantly less severe increase in triglyceride concentration. In contrast, *APOA5* c.56G>C and the 2 *APOE* variants studied seemed to have no particular association with triglyceride concentrations during bexarotene therapy. These results are in apparent contradiction to previous knowledge on the biological effects of such

Table 3. Triglyceride (TG) Concentrations Before and After Bexarotene Treatment[a]

Genetic Polymorphism	TG Concentration, Mean (SD), mg/dL		*P* Value
	Noncarriers	Carriers	
APOA5 c.-1131T>C			
TG level before treatment	121.24 (143.36)	125.66 (161.06)	.78
Maximal TG level after treatment	328.32 (188.50)	246.90 (188.50)	.12
Adjusted maximal TG level[b]	327.43 (169.91)	246.90 (172.57)	.10
APOA5 c.56G>C			
TG level before treatment	123.89 (148.67)	111.50 (130.09)	.46
Maximal TG level after treatment	312.39 (190.27)	307.96 (188.50)	.84
Adjusted maximal TG, mean (SD), mg/dL[c]	310.62 (173.45)	320.35 (176.11)	.87
APOC3 c.*40C>G			
TG level before treatment	117.70 (142.48)	147.79 (163.72)	.08
Maximal TG level after treatment	315.04 (191.15)	292.92 (181.42)	.70
Adjusted maximal TG level[d]	324.78 (171.68)	251.33 (172.57)	.14
APOE c.388T>C			
TG level before treatment	121.24 (143.36)	128.32 (161.06)	.62
Maximal TG level after treatment	311.50 (190.27)	311.50 (189.38)	>.99
Adjusted maximal TG level[d]	314.16 (172.57)	299.12 (172.57)	.76
APOE c.526C>T			
TG level before treatment	122.12 (145.13)	120.35 (153.98)	.88
Maximal TG level after treatment	319.47 (189.38)	275.22 (191.15)	.44
Adjusted maximal TG level[c]	317.70 (172.57)	284.07 (174.34)	.51
APOA5 c.1131T>C and/or *APOC3* c.*40C>G			
TG level before treatment	119.47 (144.25)	130.97 (155.75)	.45
Maximal TG level after treatment	330.97 (192.04)	253.98 (176.99)	.12
Adjusted maximal TG level[d]	330.97 (169.03)	241.59 (169.91)	.02

SI conversion factor: To convert TG to millimoles per liter, multiply by 0.0113.

[a] The analyses were performed with the natural logarithm of the maximal TG level; however, the data are shown as antilogarithm of the mean and the SD for easier comprehension. Two models have been performed to analyze the main variable (maximal TG levels): one unadjusted and the other adjusted for baseline TG levels and for variables that had shown significant differences in genotypes.

[b] Adjusted by sex and baseline TG model.

[c] Adjusted by age and baseline TG model.

[d] Adjusted by TG model.

polymorphisms in the general population. Previous studies have observed that carrying *APOA5* c.-1131T>C and *APOA5* c.56G>C minor alleles is associated with hypertriglyceridemia,[22,23] thus conferring a higher risk for coronary artery disease, stroke, and metabolic syndrome.[24]

A complete explanation for our results is difficult to establish, but a different hypothesis could be considered. Kim et al[25] showed that the *APOA5* c.-1131T>C minor allele may lead to reduced ApoA-V concentration, with concomitantly reduced lipoprotein lipase activity, resulting in higher triglyceride levels in the general population. Those authors also observed that this association was reversed when triglyceride concentrations were greater than 150 mg/dL. We believe that a similar phenomenon may partially explain our results. However, we must acknowledge limitations for this hypothesis, because we did not specifically include ApoA-V concentrations in our work and the implications of these observations in the other apolipoprotein genotypes are unknown thus far.

Another possible explanation for our results could be related to the association of some *APO* polymorphisms with the response to fenofibrate therapy. The recent Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) Study tested the association between the *APOA1*/*C3*/*A4*/*A5* gene cluster and the lipid response to 3-week fenofibrate treatment.[26] In that study, the authors observed that the minor alleles of *APOA5*_S19W (c.56G>C), *APOA4*_N147S (c.440G>A), *APOC3*_G34G (c.102T>C), and *APOC3*_3U386 (c.*40G>C) were significantly associated with an enhanced triglyceride response to fenofibrate treatment. In addition, in another branch of the GOLDN study, the association between tagged single-nucleotide polymorphisms (c.-1131T>C and c.56G>C) at *APOA5* and triglyceride and high-density lipoprotein cholesterol response to 3 weeks of fenofibrate treatment was examined in a group of 791 participants. In that study, it was observed that the minor allele carriers of the polymorphism c.56G>C presented a greater triglyceride level decrease and high-density lipoprotein cholesterol level increase in response to fenofibrate treatment compared with noncarriers.[27,28] In another recent study (B. Candás, doctoral thesis, Barcelona University, December 1, 2011) the *APOA5* c.-1131T>C, APOA5 c.56G>C, APOC3 c*40C>G, and APOE c.388T>C polymorphisms and their association with fenofibrate response were investigated. In that work, carriers of the c*40C>G of the *APOC3* gene responded to fenofibrate treatment up to 11% better than noncarriers. Because our patients were simultaneously treated with bexarotene and fenofibrate, these observations are in agreement with our data. We do not know the exact association of each polymorphism with fenofibrate therapy response; further pharmacogenomic studies are needed to address this question.

In addition to the genetic results, laboratory data obtained in this study showed that a higher baseline triglyceride concentration was associated with higher maximal triglyceride concentrations during bexarotene treatment regardless of genetic polymorphisms. This association, not previously reported, could help physicians assess which patients will experience more severe hypertriglyceridemia.

Our results also show that bexarotene is an effective treatment for CTCL, with a high overall response rate (84.5%). These data support the use of bexarotene for patients with refractory and advanced-stage CTCL. The response rate in our patients seems higher than would be expected based on previous reports.[4,20,21] We believe the greater response rate could be because almost 60% of our patients were in an early phase of the disease (stage I), in whom the response rate to bexarotene treatment is reported to be higher than for those in more advanced stages, including tumoral or erythrodermic phases. In a recent study, a Phase 3 Trial of Brentuximab Vedotin (SGN-35) vs Physician's Choice (Methotrexate or Bexarotene) in Participants With CD30-Positive Cutaneous T-Cell Lymphoma (ALCANZA),[29] the results of that clinical trial comparing brentuximab vedotin with physician's choice (bexarotene or methotrexate) in CD30-positive CTCLs showed that overall response rate lasting 4 months in the physician's choice branch was 16%. We believe that, again, these differences in response could reflect that the number of patients with early-stage disease in ALCANZA was lower than that of patients in our series. In addition, all patients in the ALCANZA trial had CD30-positive mycosis fungoides. Because there is no information about earlier particular sensitivity to bexarotene in this setting, we believe it is difficult to contrast the ALCANZA results with standard cases of mycosis fungoides in regular clinical practice.

Limitations

The findings of the present study may help physicians assess which patients will have a better lipid-profile response and, consequently, which may have a bad outcome. However, the sensitivity of these polymorphisms for anticipating bad outcomes is not yet clear, and we cannot establish which patients will need to discontinue treatment or which will experience pancreatitis. More studies should be done to investigate these questions.

Conclusions

Cutaneous T-cell lymphoma is a rare disease with a reported annual incidence of about 6.4 to 9.6 cases per million people in the United States.[6] To our knowledge, this is the largest multicenter study to date evaluating patients with CTCL treated with bexarotene and the first to focus on the role of genetic polymorphisms in bexarotene-induced hypertriglyceridemia. Our results show that patients carrying at least 1 of the minor alleles of *APOA5* c.-1131T>C or *APOC3* c.*40C>G are less likely to experience severe hypertriglyceridemia. These data suggest that *APO* polymorphism investigation could be helpful in the clinical evaluation of bexarotene-induced hypertriglyceridemia in patients with CTCL and in the identification of the most suitable candidates for this therapy.

ARTICLE INFORMATION

Accepted for Publication: August 23, 2018.

Published Online: October 24, 2018. doi:10.1001/jamadermatol.2018.3679

Author Affiliations: Cardiovascular Risk Unit, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain (Cabello, Pintó); Clinical Genetics Laboratory, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain (Alia); Dermatology Department, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain (Muniesa, Servitje); Dermatology Department, Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain (Fernandez-de-Misa); Dermatology Department, Complejo Hospitalario Universitario Insular Materno-Infantil, Las Palmas de Gran Canaria, Spain (Peñate); Dermatology Department, Hospital Universitario Virgen del Rocio, Sevilla, Spain (Morillo); Dermatology Department, Hospital General Universitario de Valencia, Valencia, Spain (Perez-Farriols); Dermatology Department, Hospital Clínic, IDIBAPS, Barcelona, Spain (Estrach); Dermatology Department, Hospital Universitario de Basurto, Bilbao, Spain (Izu); Dermatology Department, Hospital del Mar, IMIM, Barcelona, Spain (Gallardo); Dermatology Department, Hospital Universitario de Salamanca, Salamanca, Spain (Román); Dermatology Department, Hospital Nuestra Señora del Prado, Talavera, Spain (Cervigón); Dermatology Department, Hospital Arnau de Vilanova, Lleida, Spain (Ortiz-Brugues); Dermatology Department, Hospital Universitario 12 de Octubre, Institute i+12, CIBERONC, Medical School, University Complutense, Madrid, Spain (Ortiz-Romero).

Author Contributions: Dr Cabello had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; Dr Alia had full access to the genetic study data and samples and takes responsibility for the integrity of those data and the accuracy of the data analysis.
Concept and design: Cabello, Pintó, Estrach, Izu, Ortiz-Romero, Servitje.
Acquisition, analysis, or interpretation of data: Cabello, Alia, Pintó, Muniesa, Fernandez-de-Misa, Peñate, Morillo, Perez-Ferriols, Estrach, Izu, Gallardo, Román, Cervigón, Ortiz Brugues, Servitje.
Drafting of the manuscript: Cabello, Pintó, Estrach, Izu, Cervigón, Servitje.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Cabello.
Obtained funding: Cabello, Pintó, Muniesa, Servitje.
Administrative, technical, or material support: Cabello, Pintó, Muniesa, Peñate, Izu, Román.
Supervision: Cabello, Alia, Pintó, Fernandez-de-Misa, Perez-Ferriols, Izu, Gallardo, Ortiz-Romero, Servitje.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported EISAI Co LTD.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review, or approval of the manuscript; and decision to publish the manuscript for publication.

Additional Contributions: The authors thank the physicians and patients for their valuable contributions to this study. Emili Corbella, Cardiovascular Risk Unit, Hospital Universitari de Bellvitge-IDIBELL; CIBEROBN, assisted in the statistical analyses of the manuscript. He was not compensated for his work on this manuscript. The members of Experior, CRO, contracted by IDIBELL performed the tasks of protocol review, commissioning, and coordination of the collection and delivery of genetic samples to the genetic testing center of IDIBELL.

REFERENCES

1. Scarisbrick JJ, Morris S, Azurdia R, et al. U.K. consensus statement on safe clinical prescribing of bexarotene for patients with cutaneous T-cell lymphoma. *Br J Dermatol*. 2013;168(1):192-200. doi:10.1111/bjd.12042

2. Panchal MR, Scarisbrick JJ. The utility of bexarotene in mycosis fungoides and Sézary syndrome. *Onco Targets Ther*. 2015;8:367-373.

3. Whittaker SJ, Marsden JR, Spittle M, Russell Jones R; British Association of Dermatologists; U.K. Cutaneous Lymphoma Group. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. *Br J Dermatol*. 2003;149(6):1095-1107. doi:10.1111/j.1365-2133.2003.05698.x

4. Quéreux G, Saint-Jean M, Peuvrel L, Brocard A, Knol AC, Dréno B. Bexarotene in cutaneous T-cell lymphoma: third retrospective study of long-term cohort and review of the literature. *Expert Opin Pharmacother*. 2013;14(13):1711-1721. doi:10.1517/14656566.2013.810718

5. Trautinger F, Knobler R, Willemze R, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome. *Eur J Cancer*. 2006;42(8):1014-1030. doi:10.1016/j.ejca.2006.01.025

6. Wilcox RA. Cutaneous T-cell lymphoma: 2014 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2014;89(8):837-851. doi:10.1002/ajh.23756

7. Assaf C, Bagot M, Dummer R, et al. Minimizing adverse side-effects of oral bexarotene in cutaneous T-cell lymphoma: an expert opinion. *Br J Dermatol*. 2006;155(2):261-266. doi:10.1111/j.1365-2133.2006.07329.x

8. Lloret Linares C, Pelletier AL, Czernichow S, et al. Acute pancreatitis in a cohort of 129 patients referred for severe hypertriglyceridemia. *Pancreas*. 2008;37(1):13-2. doi:10.1097/MPA.0b013e31816074a1

9. Cabello I, Servitje O, Corbella X, Bardés I, Pintó X. Omega-3 fatty acids as adjunctive treatment for bexarotene-induced hypertriglyceridaemia in patients with cutaneous T-cell lymphoma. *Clin Exp Dermatol*. 2017;42(3):276-281. doi:10.1111/ced.13044

10. Lewis GF, Xiao C, Hegele RA. Hypertriglyceridemia in the genomic era: a new paradigm. *Endocr Rev*. 2015;36(1):131-147. doi:10.1210/er.2014-1062

11. Melegh BI, Duga B, Sümegi K, et al. Mutations of the apolipoprotein A5 gene with inherited hypertriglyceridaemia: review of the current literature. *Curr Med Chem*. 2012;19(36):6163-6170. doi:10.2174/092986711209066163

12. Johansen CT, Kathiresan S, Hegele RA. Genetic determinants of plasma triglycerides. *J Lipid Res*. 2011;52(2):189-206. doi:10.1194/jlr.R009720

13. Lamiquiz-Moneo I, Blanco-Torrecilla C, Bea AM, et al. Frequency of rare mutations and common genetic variations in severe hypertriglyceridemia in the general population of Spain. *Lipids Health Dis*. 2016;15:82. doi:10.1186/s12944-016-0251-2

14. Zhao T, Zhao J. Association of the apolipoprotein A5 gene -1131 T>C polymorphism with fasting blood lipids: a meta-analysis in 37859 subjects. *BMC Med Genet*. 2010;11:120. doi:10.1186/1471-2350-11-120

15. Dergunov AD. Apolipoprotein E genotype as a most significant predictor of lipid response at lipid-lowering therapy: mechanistic and clinical studies. *Biomed Pharmacother*. 2011;65(8):597-603. doi:10.1016/j.biopha.2011.04.003

16. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

17. Olsen EA, Whittaker S, Kim YH, et al; International Society for Cutaneous Lymphomas; United States Cutaneous Lymphoma Consortium; Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol*. 2011;29(18):2598-2607. doi:10.1200/JCO.2010.32.0630

18. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486-2497. doi:10.1001/jama.285.19.2486

19. ExAC Browser (Beta)/Exome Aggregation Consortium website. http://exac.broadinstitute.org/. Accessed September 21, 2018.

20. Abbott RA, Whittaker SJ, Morris SL, et al. Bexarotene therapy for mycosis fungoides and Sézary syndrome. *Br J Dermatol*. 2009;160(6):1299-1307. doi:10.1111/j.1365-2133.2009.09037.x

21. Väkevä L, Ranki A, Hahtola S. Ten-year experience of bexarotene therapy for cutaneous T-cell lymphoma in Finland. *Acta Derm Venereol*. 2012;92(3):258-263. doi:10.2340/00015555-1359

22. Pennacchio LA, Olivier M, Hubacek JA, Krauss RM, Rubin EM, Cohen JC. Two independent apolipoprotein A5 haplotypes influence human plasma triglyceride levels. *Hum Mol Genet*. 2002;11(24):3031-3038. doi:10.1093/hmg/11.24.3031

23. Talmud PJ, Hawe E, Martin S, et al. Relative contribution of variation within the APOC3/A4/A5 gene cluster in determining plasma triglycerides. *Hum Mol Genet*. 2002;11(24):3039-3046. doi:10.1093/hmg/11.24.3039

24. Oliveira Sousa M, Alía P, Pintó X. Apolipoprotein A5 gene: association with triglyceride metabolism and cardiovascular disease [in Spanish]. *Med Clin (Barc)*. 2008;130(20):787-793. doi:10.1157/13121105

25. Kim JY, Kim OY, Paik JK, Lee SH, Lee JH. Association of apolipoprotein A-V concentration with apolipoprotein A5 gene -1131T>C polymorphism and fasting triglyceride levels. *J Clin Lipidol*. 2013;7(2):94-101. doi:10.1016/j.jacl.2012.06.002

26. Liu Y, Ordovas JM, Gao G, et al. Pharmacogenetic association of the *APOA1/C3/A4/A5* gene cluster and lipid responses to fenofibrate: the genetics of lipid-lowering drugs and diet network study. *Pharmacogenet Genomics*. 2009;19(2):161-169. doi:10.1097/FPC.0b013e32831e030e

27. Lai CQ, Arnett DK, Corella D, et al. Fenofibrate effect on triglyceride and postprandial response of apolipoprotein A5 variants: the GOLDN study. *Arterioscler Thromb Vasc Biol*. 2007;27(6):1417-1425. doi:10.1161/ATVBAHA.107.140103

28. Hegele RA, Pollex RL. Apolipoprotein A-V genetic variation and plasma lipoprotein response to fibrates. *Arterioscler Thromb Vasc Biol*. 2007;27(6):1224-1227. doi:10.1161/ATVBAHA.107.144980

29. Prince HM, Kim YH, Horwitz SM, et al; ALCANZA study group. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet*. 2017;390(10094):555-566. doi:10.1016/S0140-6736(17)31266-7