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Genetic association with intravitreal ranibizumab response for neovascular age-related macular degeneration in Hispanic population

Francisco Jose Rodríguez[1,2], Hernan Andres Rios[1,2], María Camila Aguilar[1,2], Shirley Margarita Rosenstiehl[1,2], Nancy Gelvez[3], Greizy Lopez[3], Martha L. Tamayo[3]

Abstract:

BACKGROUND/PURPOSE: Age-related macular degeneration (AMD) is the leading cause of visual impairment in patients over 55 years. Currently, the most common therapies for neovascular AMD (nAMD) are intravitreal antiangiogenics. Studies suggest that genetic factors influence on antiangiogenics therapy outcomes. The purpose of this work was to establish the association between complement factor H (CFH) (Y402H), age-related maculopathy susceptibility 2 (ARMS2) (A69S), and high-temperature requirement factor A1 (HTRA1) (rs11200638) polymorphisms and the response to treatment with ranibizumab in patients with nAMD.

METHODS: A cross-sectional study with 61 eyes with nAMD treated with ranibizumab was performed. Association between polymorphisms from CFH, ARMS2, and HTRA1 with the response to treatment was established.

RESULTS: The mean age of patients was 76.6 (51–91) years. Only 37.7% of patients had a functional response and 26.2% had an anatomic response. TT polymorphism Y402H from CFH gene was associated with an increased likelihood of functional response to treatment. Otherwise, there was not a statistically significant association between anatomic and functional response to gene polymorphisms rs11200638 from HTRA1 and rs10490924 from ARMS 2.

CONCLUSIONS: This study suggests that the response to intravitreal antiangiogenic therapy with ranibizumab was not associated to main polymorphisms from genes HTRA1 and ARMS2. However, it was found that the response to treatment differed according to CFH genotype, suggesting that further investigations are needed to establish if patients with the CC and TC genotype may need to be monitored more closely for disease recurrence than the TT genotype.

Keywords:

Angiogenesis inhibitors, Hispanic Americans, macular degeneration, polymorphism

Introduction

Age-related macular degeneration (AMD) is the leading cause of visual impairment and vision loss in aging populations in industrialized countries in patients over 55 years. Advanced stages of the disease involve either the development of choroidal neovascularization (CNV) or atrophic changes in the macula.[1] Previous reports showed a prevalence of 11% in patients between 65 and 74 years and a prevalence of 28% in patients between 75 and 85 years of life.[2] In Colombia, it was found that the prevalence of advanced AMD was 4.9% and 11.8% in early presentation.[3]

Currently, the most common therapies for neovascular AMD (nAMD) are intravitreal

[1]Fundacion Oftalmologica Nacional, [2]Universidad del Rosario, School of Medicine, [3]Institute of Human Genetics, Pontificia Universidad Javeriana, Bogota, Colombia

Address for correspondence:
Dr. Francisco Jose Rodriguez, Calle 50 # 13-50, 110231 Bogota, Colombia.
E-mail: fjrodriguez@fon.org.co

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ranibizumab (Lucentis, Genentech, South San Francisco, CA, USA), aflibercept (Eylea, Bayer Pharma AG, Berlin, Germany), and bevacizumab (Avastin, Genentech, South San Francisco, CA, USA).[4] Genetic factors that influence the development of nAMD have been primarily identified through association studies with DNA sequence variants, genetic profile seems to contribute to this variability on clinical outcomes.[5-8] To date, some studies have suggested that complement factor H (CFH, polymorphism Y402H), age-related maculopathy susceptibility 2 (ARMS2, polymorphism rs10490924), high-temperature requirement factor A1 (HTRA1, polymorphism rs11200638), apolipoprotein E, and several vascular endothelial growth factor A polymorphisms are associated with outcomes after ranibizumab or bevacizumab intravitreal therapy.[7,9-15]

The purpose of this cross-sectional study was to associate CFH (Y402H), ARMS2 (rs10490924), and HTRA1 (rs11200638) polymorphisms with the response to intravitreal ranibizumab therapy in Colombian patients with nAMD.

Methods

A cross-sectional study with 61 eyes (61 patients) was performed. We included patients from an ophthalmologic reference center in Bogota (Colombia), between January 2008 and October 2015. The inclusion criteria were age older than 55 years, CNV secondary to AMD, previous treatment with at least 3 monthly intravitreal injection of ranibizumab (loading dose) and a 1-year follow-up in a Pro Re Nata regimen, best-corrected visual acuity (BCVA) records, fundus examination, and spectral-domain optical coherence tomography (SD-OCT) (Cirrus, Carl Zeiss Meditec, Dublin, CA, USA) reports in the first (previous treatment) and last visit (post-treatment). The exclusion criteria were the presence of other macular pathologies that can modify the course or treatment of AMD such as high myopia (<−8.00 spherical equivalent), occlusive vascular retinal diseases, retinal detachment, diabetic retinopathy, and retinal dystrophies. Cases in which both eyes became eligible for the study, only one eye was included. Clinical data and SD-OCT measurements before and after treatment were taken for analysis. Data included were visual acuity, slit-lamp biomicroscopy, fundus examination, and SD-OCT measurements (central retinal thickness, and presence of intra- or subretinal fluid).

The cases were divided according to functional response (based on visual acuity) and morphological response (based on SD-OCT). Functional responders were defined as a case, in which visual acuity gain was 0.1 LogMAR or more at 12 months, and morphological responders were defined as a case with 10% decrease in foveal central thickness with the absence of intra- or subretinal fluid by SD-OCT at 12 months. Cases that did not meet these requirements were functional or morphological nonresponders, respectively. Approval was obtained from the Institutional Review Board of National Ophthalmological Foundation (Approval No. CEI156/2013). Research adhered to the Tenets of the Declaration of Helsinki, and all patients provided written informed consent before participation.

Genetic study

Candidate genes for analysis were selected from previous reports of AMD-associated genes, including CFH, ARMS2, and HTRA1. The study exons where focus in polymorphisms that have shown association with AMD in different previous populations. Blood samples from 61 patients were available for genotyping; all samples produced sufficiently high-quality DNA for genotypic analysis. Peripheral blood sample by venipuncture was taken to each patient once informed consent was signed. DNA extraction was performed by the phenol-chloroform method, and the bidirectional sequencing was carried out in the sequencer ABI 3130. The sequences were analyzed with the SeqScape software, ThermoFisher Scientific Inc, Waltham, Massachusetts, US.

For this study, genotyping distribution from the study patients was compared with genotyping distribution from one hundred healthy individuals, and it was considered for validating the frequency of the polymorphisms found. This validation is necessary in all genetic studies when polymorphism frequency in the healthy population is not known.

Statistics

Statistical analysis was performed in IBM SPSS Statistics version 21 (ser. 572110343, Armonk, New York, US). Univariate analysis was performed; for categorical variables, we used the frequency distribution, and for quantitative variables, we calculated measures of central tendency and dispersion (mean and range) according to the relevance for each variable analyzed. Subsequently, the frequency of polymorphism in patients was calculated with and without treatment response. The bivariate analysis included measurement calculated from the factor of interest (presence of polymorphism) and the event (response to treatment), as odds ratio (OR). The association analysis was determined by Chi-square test.

The calculation of the sample size was performed in the Epidat statistical program Version 4.0 (Maipú, Argentina). The parameters were a risk of exposition 38%, risk of no exposition 11%,[6] exposed and no-exposed reason 1, confidence interval 95%, power 80% and losses 10%, for a total of 61 study patients.

Results

Sixty-one patients were selected. The mean age (range) of patients was 76.6 (51–91) years, 54% were female. In general, consanguinity was present only in 8.2% of cases [Table 1]. Thirty-seven percent of participants had an anatomical response, with mean number of intravitreal injections of 8.2 [Table 2]. The mean subfoveal central thickness (SFT) prior treatment was 364 µ and after treatment was 214 µ. Mean BCVA prior treatment was 1.20 logMAR, and after intravitreal injection was 0.95. Regarding functional response, 26.2% of patients had a functional response, with mean number of intravitreal injections of 6.8. The mean SFT was 303 µ prior treatment and 255 µ after antiangiogenic treatment. For visual acuity, the mean BCVA prior treatment was 1.0 logMAR, with a mean BCVA after treatment of 0.52 logMAR [Table 3].

In regard to the molecular results, a total of 61 individuals produced sufficiently high-quality DNA for genotypic analysis. The genotypes distribution was compared with healthy individuals (Database from Instituto de Genetica Humana, Pontificia Universidad Javeriana, Bogotá, Colombia). It was found a similar distribution on CFH (Y402H) genotypes as seen on healthy individuals, with subtle differences on distribution of ARMS2 (rs10490924) and HTRA1 (rs11200638) genotypes [Table 4]. Furthermore, it was observed that a second additional polymorphism (rs61544945) on gen ARMS2 had an identical pattern distribution than polymorphism rs10490924. The differentiation between both ARMS2 polymorphisms was made just because the rs61544945 polymorphism had zones with deletions. These single-nucleotide polymorphisms (SNP) were present in the studied individuals as in healthy control population [Table 4].

The studied population had 16 (26.2%) and 23 (37.7%) cases with favorable anatomical and functional response, respectively to treatment with ranibizumab. The rest of the cases had no response to treatment [Table 5]. The homozygote genotype TT on polymorphism rs10490924 (ARMS2 gen), the genotype TG on polymorphism rs61544945 (ARMS2 gen), and homozygote genotype AA on polymorphism rs11200638 (HTRA1 gen) seemed to have a lower probability of functional and anatomical response, although this finding was not statistically significant.

On CFH (Y402H) polymorphism, 44.3% of patients were TT, 47.5% were TC, and 4.9% were CC, with only 3.3% without amplification. On this polymorphism, there was an association between the C allele and the absence of functional response to treatment with ranibizumab [Table 5]. The total of the patients who had the CC polymorphism showed no specific functional response; however, the number of patients in this subgroup was small (n = 3). TT polymorphism

Table 1: General characteristics

n=61 patients with neovascular AMD
Age±SD: 76.6±8
Female: 54%, male: 46%
Mean number of injections±SD: 8.2±6
Nonconsanguinity 91.8%

AMD: Age-related macular degeneration, SD: Standard deviation

Table 2: Characteristics of the responders and nonresponders

	Responders		Nonresponders	
	Anatomic	Functional	Anatomic	Functional
Number of patients	16	23	45	38
Mean number of injections±SD	8.2±4.4	6.8±3.4	8.3±3.2	9.1±3.4
CNV type (Type 1/Type 2) (%)	62.5/37.5	60.8/39.2	68.8/31.2	71.0/29.0
Baseline BCVA, LogMar±SD	1.20±0.9	1.00±0.7	0.83±0.5	0.84±0.6
Final BCVA, LogMar±SD	0.95±0.6	0.53±0.4	0.77±0.5	0.98±0.6

CNV: Choroidal neovascularization, BCVA: Best-corrected visual acuity, SD: Standard deviation

Table 3: Characteristics of the responders

	Anatomic responders (n=16)	Functional responders (n=23)	Anatomic and functional responders (n=11)
Mean age±SD	76±8	75±9	77.5±10
Female/male (%)	62.5/37.5	69/30.4	72.7/27.3
Mean number injections±SD	8.2±4.4	6.8±3.4	8.5±4.4
Nonconsanguinity (%)	93.8	91.3	82.0
Mean SCT prior±SD	364±112 µm	303±76 µm	334±89 µm
Mean SCT post±SD	214±45 µm	255±60 µm	227±38 µm
Mean BCVA prior±SD	1.20±0.9	1.00±0.7	1.52±1.1
Mean BCVA post±SD	0.95±0.6	0.53±0.4	0.80±0.6

SCT: Subfoveal central thickness, BCVA: Best-corrected visual acuity, SD: Standard deviation

was associated with increased likelihood functional response with an OR of 0.389 (IC 0.178–0.852, $P = 0.01$) [Table 6].

Other measurements showed no association. There was no statistically significant association between consanguinity and anatomical and functional response ($P = 1.0$). No association was found between age and functional response ($P = 0.5$), and there was no statistically significant association between central macular thickness and functional response.

Table 4: Genotypes distribution on healthy and cases subjects

Gen	Genotypes	Healthy (%)	Cases (%)
CFH	TT	51.3	44.3
	TC	32.8	47.5
	CC	0.8	4.9
	N/A	15.1	3.3
ARMS2 pol 1 rs10490924 (A69S)	GG	44.5	29.5
	GT	30.3	29.5
	TT	9.2	27.9
	N/A	16.0	13.1
ARMS2 pol 2 rs61544945 (insTG)	--/--	44.5	29.5
	TG/--	30.3	29.5
	TG/TG	9.2	27.9
	N/A	16.0	13.1
HTRA1	GG	44.5	26.2
	GA	30.3	37.7
	AA	9.2	27.9
	N/A	16.0	8.2

N/A: Not amplified

Discussion

This is the first study about the response to antiangiogenic intravitreal treatment and associated polymorphisms in Hispanic population. The current study suggests that the response to intravitreal antiangiogenic treatment with ranibizumab was not dependent on the heterozygous SNPs on rs11200638 (HTRA1 gen) and rs10490924 and rs61544945 (ARMS2 gen). However, homozygote genotypes TT (for ARMS2 rs10490924) and AA (for HTRA1 gen) seemed to have a lower probability of functional and anatomical response; nevertheless, this finding was not statistically significant. Polymorphisms in the promoter region of the HTRA1 gene have been related to increase susceptibility to AMD in previous studies, especially the neovascular form,[16] otherwise, no relation was found between HTRA1 polymorphism and treatment response in the present study. A meta-analysis made by Hu showed that rs10490924 (ARMS2) appeared to be a predictor for antiangiogenic response in East Asian population; however, no statistical significance was found in the Caucasian subgroup analysis.[15] The conception that simply genotyping in individuals without consideration of their ethnicity is not accurate in assessing the individuals risk for AMD could also explain the different results worldwide when assessing the response to antiangiogenic agents.[17] Finally, all previous findings support the population-based genotype as a key factor in the response to antiangiogenic therapy.

Table 5: Genotypes distribution

		Anatomical				Functional			
	Polymorphism	*n* (%)	Responders (%)	No Responders (%)	*P*	*n* (%)	Responders (%)	No Responders (%)	*P*
Gen ARMS2 rs10490924	NA	8 (13.1)	1 (12.5)	7 (87.5)	0.46	8 (13.1)	5 (62.5)	3 (37.5)	0.16
	GG	18 (29.5)	7 (38.9)	11 (61.1)		18 (29.5)	9 (50)	9 (50)	
	GT	18 (29.5)	5 (27.8)	13 (72.2)		18 (29.5)	5 (27.8)	13 (72.2)	
	TT	17 (27.9)	3 (17.6)	14 (82.4)		17 (27.9)	4 (23.5)	13 (76.5)	
	Total	61 (100)	16 (26.2)	45 (73.8)		61 (100)	23 (37.7)	38 (62.3)	
Gen ARMS2 rs61544945	NA	8 (13.1)	1 (12.5)	7 (87.5)	0.46	8 (13.1)	5 (62.5)	3 (37.5)	0.16
	-.-	18 (29.5)	7 (38.9)	11 (61.1)		18 (29.5)	9 (50)	9 (50)	
	TG/-.-	18 (29.5)	5 (27.8)	13 (72.2)		18 (29.5)	5 (27.8)	13 (72.2)	
	TG/TG	17 (27.9)	3 (17.6)	14 (82.4)		17 (27.9)	4 (23.5)	13 (76.5)	
	Total	61 (100)	16 (26.2)	45 (73.8)		61 (100)	23 (37.7)	38 (62.3)	
Gen HTRA1 rs11200638	NA	5 (8.2)	2 (40)	3 (60)	0.5	5 (8,2)	1 (20)	4 (80)	0.55
	GG	16 (26.2)	6 (37.5)	10 (62.5)		16 (26.2)	8 (50)	8 (50)	
	GA	23 (37.7)	5 (21.7)	18 (73.8)		23 (37.7)	9 (39.1)	14 (60.9)	
	AA	17 (27.9)	3 (17.6)	14 (82.4)		17 (27.9)	5 (29.4)	12 (70.6)	
	Total	61 (100)	16 (26.2)	45 (73.8)		61 (100)	23 (37.7)	38 (62.3)	
Gen CFH Y402H	NA	2 (2.2)	1 (50)	1 (50)	0.71	2 (2.2)	1 (50)	1 (50)	0.01
	TT	27 (44.3)	6 (22.2)	21 (77.8)		27 (44.3)	16 (59.3)	11 (40.7)	
	TC	29 (47.5)	8 (27.6)	21 (72.4)		29 (47.5)	6 (20.7)	23 (79.3)	
	CC	3 (4.9)	1 (33.3)	2 (66.7)		3 (4.9)	0 (0)	3 (100)	
	Total	61 (100)	16 (26.2)	45 (73.8)		61 (100)	23 (37.7)	38 (62.3)	

NA: Not amplified

Table 6: TT polymorphism (CFH gene) estimated risk for functional responders

	Value	CI		*P*
		Inferior	Superior	
Responders	0.389	0.178	0.852	0.01
Nonresponders	1.692	1.119	2.557	

CI: Confidence interval

Regarding the CFH gene and its allele risk C, it showed similar results as was reported by Lee *et al*.,[11] evidencing that this allele (with its combination TC or CC) is associated with a lack of anatomical and functional response. Contrary, the presence of TT polymorphism was associated with good anatomical and functional response to ranibizumab. CFH plays a central role in the modulation of the complement alternative pathway by facilitating C3b degradation by the plasma serine protease factor I and enhancing C3 convertase dissociation,[18] additional role attributed to CFH is binding to heparin and C-reactive protein.[19] This is crucial to protect the tissues from excess complement activation and complement-mediated vascular injury after exposure to agents (molecules and other cellular pro-inflammatory components) that can activate the alternative pathway.[20] Consistently, reducing the bioavailability or activity of CFH, due to genetic mutations or polymorphisms, can cause uncontrolled activation of the complement pathway and consequent persistent vascular damage, resulting in a probable poor response to antiangiogenic treatments. In the report by Lee *et al*., patients with risk allele C needed more injections of ranibizumab during the study period due to the absence of adequate response to treatment.[11] Our study found a potential pharmacogenetic association between CFH (Y402H) genotypes and low efficacy of ranibizumab therapy for functional response. The polymorphism Y402H of the complement factor H is the most consistently found genetic susceptibility locus for both AMD forms and most ethnic groups. With the exception of several Asian study populations, individuals who carry the risk allele C (leading to the amino acid histidine at position 402) are between 2.4 and 4.6 times more likely to be affected by AMD, even likely to have a decreased in any response to treatment with antiangiogenic agents.[21] Similar conclusion about CFH polymorphism (Y402H) was made in a retrospective analysis from the age-related eye disease study (AREDS), where individual's response to AREDS supplements was related to CFH genotype.[14] The biological plausibility to support the lack of response to treatments (supplements and antiangiogenics) in patients with C allele risk on polymorphism Y402H is based in that the CFH dysfunction may lead to excessive inflammation and tissue damage involved in the pathogenesis of AMD itself.[22,23] These results may imply that the strong genetic predisposition to AMD conferred by the C allele genotype limits the benefits available from different treatments in all spectral disease. This conclusion could also apply for Hispanic patients with C allele risk.

Within the limitations of this study, a significant number of patients had a delayed onset of treatment, this could influenced the results of the VA outcomes (functional response), and the observed effects could potentially be based on the pathophysiology of natural disease rather than a true lack of pharmacogenetic effect.

Conclusions

We describe here the association of a pharmacogenetic effect of the genes CFH (Y402H), ARMS2 (rs10490924 and rs61544945), and HTRA1 (rs11200638) variations with ranibizumab in exudative AMD. It was found that the response to treatment of AMD with ranibizumab was neither associated with genes ARMS2 nor HTRA1, but differed according to CFH genotype. Further investigations are warranted to see if patients with the CC and TC genotype may need to be monitored more closely for disease recurrence than the TT genotype. This is because CC and TC genotypes had a decrease chance of positive treatment outcome. This could have clinical relevance by predicting treatment outcomes and potentially preventing unwanted side effects in those who may not benefit. Comparative studies are needed to confirm this association before any recommendation for genetic screening or change in current treatment with ranibizumab could be made.

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Conflicts of interest

The authors declare that there are no conflicts of interest of this paper.

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