UNIVERSIDADE FEDERAL DE MINAS GERAIS
Tereza Cristina Moreira Kanadani

ANÁLISE DA MICROESTRUTURA MACULAR PELA TOMOGRAFIA DE COERÊNCIA ÓPTICA DE PACIENTES PORTADORES DE DEGENERAÇÃO MACULAR RELACIONADA À IDADE TRATADOS COM ANTIANGIOGÊNICOS

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Tese apresentada ao Curso de Pós-Graduação em Medicina da Universidade Federal de Minas Gerais, como requisito parcial à obtenção do título de Doutor em Medicina.

Área de concentração: Oftalmologia.

Orientador: Prof. Dr. Márcio Bittar Nehemy.

Co-orientador: Dr. Carlos Eduardo dos Reis Veloso

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LISTA DE ABREVIATURAS:

AICV:	Angiografia com indocianina verde
AV:	Acuidade visual
AVM:	Adesão vitreomacular
DMRI:	Degeneração macular relacionada à idade
DVP:	Descolamento do vítreo posterior
EDI:	Imagem de profundidade aumentada
EMC:	Espessura macular central
ESC:	Espessura subfoveal da coroide
IVM:	Interface vitreomacular
OCT:	Tomografia de coerência óptica
PCV:	Vasculopatia polipoidal da coroide
RAP:	Proliferação angiomatosa da retina
SD:	Domínio espectral
VEGF:	Fator de crescimento do endotélio vascular

SUMÁRIO

INTRODUÇÃO:

A Degeneração Macular Relacionada à Idade (DMRI) é considerada, atualmente, a maior causa de cegueira legal nos países industrializados.[1-4] Estudos revelam que a prevalência da DMRI pode ocorrer em 1,2% dos pacientes com menos de 65 anos de idade, 7% entre 65 e 74 anos e, aproximadamente, em 20% dos pacientes com idade superior aos 75 anos.[4-5] Globalmente, é a terceira causa de cegueira legal, representando 8,7% dos casos.[6] A perda visual ocorre principalmente nas formas avançadas da doença.[7] A DMRI exsudativa ou neovascular é caracterizada pelo crescimento de vasos coroideanos neoformados, associado ao vazamento de fluidos, lípides e sangue na retina sensorial e, consequentemente, à formação de cicatriz fibrosa na mácula.[8]

A angiografia com indocianina verde (AICV) é um exame de imagem com luz infravermelha, que penetra através do epitélio pigmentar retiniano e permite a identificação e o estudo detalhado dos vasos coroideanos.[9] A utilização da AICV permitiu o reconhecimento da DMRI neovascular como amplo espectro de doenças que inclui lesões distintas, tais como a vasculopatia polipoidal coroideana (PCV) e a proliferação angiomatosa retiniana (RAP),[10,11] afecções essas com características peculiares e distintas, além das lesões neovasculares típicas. O advento da tomografia de coerência óptica (OCT) proporcionou análises em alta resolução de cortes transversais da retina, enriquecendo a compreensão dos subtipos de DMRI.[12]

Em estudo recente, nosso grupo de pesquisa avaliou uma amostra brasileira com ascendência predominantemente caucasiana e polimorfismos genéticos semelhantes aos observados em pacientes americanos e europeus. Do total de 265 olhos avaliados, 166 (62,6%) foram diagnosticados com DMRI típica, 65 (24,5%) com PCV e 34 (12,8%) com RAP.[13]

Os agentes anti-fator de crescimento do endotelial vascular (VEGF), tais como bevacizumabe, ranibizumabe e aflibercepte são o padrão-ouro para o tratamento da DMRI neovascular.[14] No entanto, alguns pacientes são não

respondedores, mostrando resistência aos agentes anti-VEGF.[15,16] Estudos recentes avaliaram a importância de polimorfismos genéticos e sugeriram que alguns polimorfismos estão associados a uma resposta terapêutica subóptima em alguns pacientes com DMRI. [17,18]

Poucos estudos avaliaram a influência da adesão vitreomacular (AVM) na resposta ao tratamento com agentes anti-VEGF.[16,19-27] A maioria deles sugeriu que os olhos com AVM apresentaram pior acuidade visual (AV) ou necessitaram de mais injeções intravítreas. A maioria desses estudos envolveu amostras de população que incluíram todos os subtipos de DMRI, inclusive a PCV. É sabido que a PCV pode ser relativamente resistente ao anti-VEGF isoladamente, razão pela qual tem sido proposto que seu tratamento envolva a associação de terapia fotodinâmica ao anti-VEGF.[28] Adicionalmente, um estudo prévio analisou pacientes com PCV separadamente e mostrou que, ao contrário da DMRI forma típica, a AVM não estava associada ao prognóstico visual. [20]

Seria assim desejável que, para avaliar a importância da interface vitreomacular na resposta aos anti-VEGF, os pacientes com DMRI fossem avaliados sem a inclusão de pacientes com PCV.

Com isso, resolvemos realizar o primeiro trabalho com o objetivo de investigar prospectivamente o efeito da AVM sobre o resultado do tratamento anti-VEGF em pacientes com DMRI neovascular sem a inclusão de pacientes com PCV por seu comportamento clínico específico e abordagem terapêutica diferente.

A adesão vitreomacular (AVM) parece ser um fator importante no desenvolvimento de patologias maculares, incluindo a DMRI.[29] Estudos anteriores consideraram a AVM persistente como possível fator de risco para o desenvolvimento da DMRI neovascular, enquanto o descolamento do vítreo posterior (DVP) parece proteger contra essa forma da doença. [29-31] Uma análise recente de estudo multicêntrico, randomizado, duplo mascarado, também mostrou que a configuração da interface vitreomacular (IVM) parece ter efeito

importante no prognóstico visual e necessidade de retratamento em casos de DMRI neovascular. Pacientes com DVP necessitaram de menor número de tratamentos do que pacientes com adesão vitreomacular.[16]

Ainda não está estabelecido se a injeção intravítrea de inibidores do VEGF, por si e isoladamente, pode induzir DVP. Apenas um estudo prévio tinha avaliado sua ocorrência após injeção de drogas intravítreas para diferentes patologias maculares e mostrou que esse procedimento pode favorecer a ocorrência de DVP.[32] Portanto, o DVP possivelmente induzido por injeção intravítrea poderia beneficiar a resposta ao tratamento. Por essa razão, resolvemos realizar o segundo trabalho com o objetivo de avaliar a incidência de DVP induzida por injeções intravítreas de agentes anti-VEGF em casos de DMRI neovascular.

Avanços na tomografia de coerência óptica de domínio espectral (OCT-SD) facilitaram a formação de imagens transversais da retina com resolução adequada, o que melhorou nossa compreensão dos subtipos de DMRI.[10-12] A imagem detalhada da secção transversal da coroide também foi recentemente obtida pelo uso do dispositivo com imagens de profundidade aumentada (EDI).[33] Nos casos de DMRI neovascular, a medição da espessura da coroide por esse método parece ser importante não apenas para o diagnóstico, mas também para a avaliação da intervenção terapêutica.[34-39]

Em alguns estudos, os pacientes com DMRI apresentaram espessura de coroide reduzida em comparação ao grupo controle.[40,41] Além disso, diferentes subtipos de DMRI têm características distintas. Recentemente, alguns pesquisadores relataram que a espessura subfoveal da coroide (ESC) é maior nos olhos com PCV que nos olhos com DMRI forma típica.[42,43] Além disso, os olhos com RAP tiveram uma ESC significativamente mais fina em comparação aos olhos normais. Características desses casos podem estar relacionadas ao mecanismo patológico da RAP.[44] Alguns estudos avaliaram a espessura da coroide após tratamento com agentes antiangiogênicos, mas com resultados controversos.[37,39,41,42,45,46,47,48] Recentemente, a ESC foi relatada como fator

preditivo para o prognóstico visual e a resposta ao tratamento na DMRI neovascular forma típica.[45] Até onde sabemos, nenhum estudo prévio avaliou a relação entre ESC e o prognóstico visual em diferentes subtipos de DMRI. Considerando esses fatos, idealizamos o terceiro trabalho com o intuito de avaliar a mudança na ESC após o tratamento antiangiogênico nos subtipos de DMRI e avaliar a relação entre essas alterações e o prognóstico visual durante o período de doze meses de seguimento utilizando EDI-OCT.

OBJETIVOS DO PRIMEIRO TRABALHO:

PRINCIPAL:

- Investigar prospectivamente a influência da AVM na resposta terapêutica do tratamento anti-VEGF em pacientes com DMRI neovascular sem a inclusão de pacientes com PCV por seu comportamento clínico específico e abordagem terapêutica diferente.

SECUNDÁRIO:

-Detectar eventuais diferenças na AVM de acordo com características dos pacientes como idade, sexo, estado do cristalino, tabagismo e tipo de tratamento.

O primeiro trabalho “Influence of vitreomacular adhesion on anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration” foi publicado na revista *Ophthalmic Research* em 2017 e encontra-se a seguir precedido pelo seu resumo em português.

RESUMO DO PRIMEIRO TRABALHO:

TÍTULO**:** Influência da adesão vitreomacular na resposta ao tratamento com agentes anti-VEGF na degeneração macular relacionada à idade (DMRI) forma neovascular.

OBJETIVO**:** Investigar o efeito da adesão vitreomacular (AVM) sobre o resultado do tratamento antiangiogênico na degeneração macular relacionada à idade (DMRI) neovascular.

MATERIAL E MÉTODOS: Noventa e nove olhos de 83 pacientes foram incluídos nesse estudo de coorte. Avaliaram-se prospectivamente a melhor acuidade visual corrigida e a espessura macular central (EMC) em pacientes com DMRI neovascular no início do estudo, um, dois, três, seis e doze meses após o tratamento com agentes anti-fator de crescimento endotelial vascular (VEGF). Todos os pacientes foram estratificados por tomografia de coerência óptica de domínio espectral em dois grupos: AVM (+) e AVM (-), de acordo com a presença ou ausência de AVM, respectivamente, e a resposta ao tratamento foi avaliada.

RESULTADOS**:** Cinquenta e quatro olhos (54,5%) foram incluídos no grupo AVM (-) e 45 olhos (45,5%) no grupo AVM (+). Em comparações pareadas de AV entre o *baseline* e cada visita de seguimento (um, dois, três, seis e doze meses), o grupo AVM (-) apresentou melhora estatisticamente significativa nos meses 1, 2 e 3 quando comparado ao *baseline* e a AV melhorou significativamente apenas no mês 3 no grupo AVM (+). Para ambos os grupos, comparações pareadas de EMC mostraram diminuição estatisticamente significativa quando os dados obtidos nos meses 1, 2, 3, 6 e 12 foram comparados ao valor basal ($p<0,05$).

CONCLUSÕES: A AVM posterior está associada a pior resultado de curto prazo em pacientes com DMRI neovascular tratada com agentes anti-VEGF.

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Influence of Vitreomacular Adhesion on Anti-Vascular Endothelial Growth Factor Treatment for Neovascular Age-Related Macular Degeneration

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Keywords
Vitreomacular adhesion · Antiangiogenic treatment · Neovascular age-related macular degeneration

Abstract

Purpose: To investigate the effect of vitreomacular adhesion (VMA) on the outcome of antiangiogenic treatment for neovascular age-related macular degeneration (AMD). ***Methods:*** Ninety-nine eyes of 83 patients were used in our cohort study. We prospectively evaluated best corrected visual acuity (BCVA) and central retinal thickness (CRT) in patients with neovascular AMD at baseline and 1, 2, 3, 6, and 12 months after treatment with anti-vascular endothelial growth factor (anti-VEGF) agents. All patients were stratified by spectral domain optical coherence tomography into 2 groups (i.e., VMA[+] and VMA[–]) according to the presence or absence of VMA, and the response to treatment was evaluated. ***Results:*** Fifty-four eyes (54.5%) were included in the VMA(–) group and 45 eyes (45.5%) comprised the VMA(+) group. In paired comparisons of mean BCVA between baseline and each follow-up visit (1, 2, 3, 6, and 12 months), the VMA(–) group showed statistically significant improvement at 1, 2, and 3 months compared to baseline, and BCVA significantly improved only at 3 months in the VMA(+) group. For both groups, paired comparisons of CRT showed a statistically significant decrease when data obtained at 1, 2, 3, 6, and 12 months were compared to baseline values ($p < 0.05$). ***Conclusions:*** Posterior VMA is associated with a worse short-term outcome in patients with neovascular AMD treated with anti-VEGF agents.

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in industrialized countries [1]. Early AMD is characterized by drusen and/or pigmentary abnormalities, whereas the late (advanced) form of AMD can lead to severe visual impairment and can be classified as atrophic (geographic atrophy) or neovascular [2]. Neovascular AMD has more recently been recognized as a broad spectrum of diseases that includes distinct subtypes such as polypoidal choroidal vasculopathy (PCV) and retinal angiomatous proliferation (RAP) [3, 4]. The pathogenesis and risk factors for the development of AMD are not completely understood [5]. Previous studies have described the relationship between the posterior vitreous and the macula in AMD. Persistent vitreomacu-

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lar adhesion (VMA) is considered a risk factor for the development of neovascular AMD, whereas posterior vitreous detachment (PVD) may protect against this form of the disease [6–8]. However, the association between VMA and PCV is not evident [9].

Abnormal VMA may also play a role in the response to treatment of neovascular AMD. Anti-vascular endothelial growth factor (anti-VEGF) agents, such as bevacizumab, ranibizumab, and aflibercept, are the gold standard for treatment of neovascular AMD [10]. However, some patients are nonresponders, showing resistance to anti-VEGF agents [11]. For juxtafoveal and subfoveal PCV, a recent guideline suggested that this form of the disease should be treated with combination treatment using photodynamic therapy and anti-VEGF in order to provide a synergistic effect of angio-occlusion and anti-angiogenesis [12]. Genetic and vitreomacular interface studies have been conducted to determine which eyes respond better to treatment [13, 14].

Few studies have evaluated the influence of VMA on the response to anti-VEGF agents [15–24]. Most of them suggested that eyes with VMA had worse visual outcomes or required more intravitreal injections. The majority of these studies involved population samples that included all AMD subtypes. Just one previous study analyzed patients with PCV separately and showed that, unlike typical AMD, VMA was not associated with the visual outcome [17].

The aim of the present study is to prospectively investigate the effect of VMA on the outcome of anti-VEGF treatment in patients with neovascular AMD without the inclusion of patients with PCV because of their specific clinical behavior and different first-line therapeutic approach.

Methods

Study Design

All of the subjects of this prospective study were informed of the nature of the study, and the research adhered to the tenets of the Declaration of Helsinki. The ethics committees of both the Institute of Vision and the Federal University of Minas Gerais in Belo Horizonte, Brazil, approved this study.

Patients

All patients with AMD diagnosed from March 2009 to December 2014 at the Institute of Vision underwent a complete ophthalmologic examination, including slit lamp biomicroscopy, color fundus photography, fluorescein angiography, and optical coherence tomography (OCT). Inclusion criteria were: (a) age ≥50 years; (b) diagnosis of neovascular AMD; (c) indication for treatment with bevacizumab, ranibizumab, or aflibercept in either eye; (d) follow-up for a minimum of 12 months; and (e) visual acuity ≥20/400. Exclusion criteria were: (a) patients with PCV; (b) choroidal neovascularization secondary to any cause except for AMD; (c) concomitant inflammatory ocular disease; (d) eyes that had undergone vitrectomy; (e) eyes with other conditions known to affect the vitreomacular interface, such as retinal vascular disease, pathologic myopia, and diabetic retinopathy; (f) patients with vitreomacular traction syndrome as defined by the International Vitreomacular Traction Study [25]; and (g) other ocular conditions that may affect visual acuity.

AMD Subtypes

Indocyanine green (ICG) angiography was performed when neovascular AMD subtypes PCV and RAP were suspected. The diagnostic criteria for PCV were based on a previous study and included data from the fundus examination, ICG angiographic findings, or both [26]. Definite cases of PCV should have early subretinal focal ICG angiogram hyperfluorescence (i.e., hyperfluorescence appears within the first 6 min after the ICG injection) and at least one of the following angiographic or clinical criteria: (a) the hyperfluorescence is associated with a branching vascular network; (b) presence of a pulsatile polyp; (c) a nodular appearance when viewed stereoscopically; (d) the presence of a hypofluorescent halo in the first 6 min; (e) the presence of orange subretinal nodules in the stereoscopic color fundus photograph; and (f) the hyperfluorescence is associated with massive submacular hemorrhage (defined as a hemorrhage of at least 4 disk areas). The diagnostic criteria for RAP were based on a previous study and included data from the fundus examination, a fluorescein angiography, and a ICG angiogram [4]. Definite cases should have the following findings: (a) preretinal, intraretinal, or subretinal hemorrhages; (b) intraretinal edema; (c) the presence of retinal dilated perfusing arterioles or draining venules or the presence of serous pigment epithelium detachment; and (d) the presence of focal ICG angiogram hyperfluorescence (i.e., "hot spot") and a retinal-retinal anastomosis or a retinal-choroidal anastomosis. Patients with neovascular AMD without signs that would lead to a diagnosis of PCV or RAP were diagnosed with typical AMD.

Anti-VEGF Treatment

Intravitreal anti-VEGF injections were performed using bevacizumab (1.25 mg/0.1 ml, Avastin®; Genentech Inc.), ranibizumab (0.5 mg/0.05 mL, Lucentis®, Genentech Inc.), or aflibercept (40 mg/ml, Eylea®; Bayer). All intravitreal anti-VEGF injections were performed in the operating room, with an aseptic technique, including the prophylactic use of topical iodopovidone 5%. All patients were subjected to a treatment protocol that included a loading dose with 3 intravitreal injections at 1-month intervals. After the third dose, they followed a pro re nata regimen. The criteria for administration of bevacizumab versus ranibizumab versus aflibercept was defined by the retinal specialist. Retreatment criteria were: (a) persistence or increase of intra- or subretinal fluid; (b) increase in RPE detachment; (c) worsening of at least one line of visual acuity; and (d) new subretinal hemorrhage. Furthermore, after the first injection, there was the possibility of exchange of the intravitreous drug in some cases. All intravitreal injections were performed by a single retinal specialist (M.B.N.).

Table 1. Baseline characteristics of patients with neovascular AMD according to the presence of VMA

	VMA(+)	VMA(–)	*p* value
Age (median), years	70.3±10.0 (79)	75.6±7.0 (76.5)	0.020[a]
Gender (M/F)	24/21	18/36	0.06[b]
Cigarette smokers (yes/no)	10/35	16/38	0.60[a]
Lens status (phakic/pseudophakic)	29/16	31/23	0.53[b]
Type of AMD (typical AMD/RAP)	40/5	46/8	0.767[b]
Treatment (bevacizumab/ranibizumab/Eylea)	19/25/1	27/22/5	0.06[b]
Baseline BCVA (logMAR)	0.49±0.29	0.52± 0.28	0.62[a]
Median baseline BCVA (logMAR)	0.50 (0.30–0.65[c])	0.50 (0.30–0.90)	
Baseline CRT, μm	357.62±111	333.50±97	0.184[a]
Median baseline CRT, μm	337.00 (290.00–397.5[c])	302.50 (260.75–379.50)	

Values are presented as means ± SD or ratios unless otherwise stated. AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CRT, central retinal thickness; F, female; logMAR, logarithm of the minimal angle of resolution; M, male; RAP, retinal angiomatous proliferation; VMA, vitreomacular adhesion. [a] Mann-Whitney test. [b] Fisher test. [c] Q1 to Q3.

Detection of VMA

All eyes were classified into 2 groups based on spectral domain OCT (Spectralis OCT™; Heidelberg Engineering, Heidelberg, Germany) analysis: VMA present and VMA absent. The VMA(+) group included patients who presented adhesion of the posterior hyaloid involving the macular region (area: 8.8 × 5.9 mm, 30° × 20°, 25-scan pattern). Patients with VMA were classified according to the diameter of the vitreous attachment to the macular surface measured by OCT, with attachment of 1,500 μm or less defined as focal and attachment of more than 1,500 μm as broad. The VMA(–) group included patients with a detached posterior hyaloid. If the vitreous boundary was not visible in the entire scan set, anteposition of the boundary beyond the scanning range was assumed, and the patient was considered to have PVD and was included in the VMA(–) group. Certified OCT technicians acquired the OCT scans, and 3 retinal specialists (T.C.M.K., C.E.V., and M.B.N.) analyzed the results. Each retinal physician was masked to the classification determined by the other. If there was any disagreement, they evaluated the data simultaneously and came to a consensus.

Visual Acuity and Central Retinal Thickness Measurement

Best-corrected visual acuity (BCVA) and central retinal thickness (CRT) were measured at baseline and 1, 2, 3, 6, and 12 months after the initial anti-VEGF treatment. BCVA was determined using a Snellen chart and then converted to a logarithm of the minimal angle of resolution values. CRT was measured based on the central 1-mm subfield thickness obtained from the spectral domain OCT analysis. Automated segmentation of retinal boundaries was used, and in case of any segmentation error it was corrected manually.

Statistical Analysis

Categorical data were assessed using the χ^2 or Fisher test. The study data were tested for a normal distribution using the Shapiro-Wilk test, which revealed that data were not normally distributed. As a result, we used a nonparametric test for comparison of continuous variables between groups (Mann-Whitney test). In addition, the Wilcoxon test was used to compare follow-up and baseline data within a treatment group. Predictive Analytics Software (PASW 18) was used for all analyses. $p < 0.05$ was considered statistically significant.

Results

Of a total of 265 eyes of 207 patients diagnosed with neovascular AMD, 166 eyes (62.6%) were diagnosed with typical AMD, 65 (24.5%) with PCV, and 34 (12.8%) with RAP. Ninety-nine eyes of 83 patients met the eligibility criteria and were included in this study. Eighty-six eyes were diagnosed with typical AMD, 13 eyes had RAP, and 27 eyes had PCV. Of the 27 eyes diagnosed with PCV, 11 showed extrafoveal polyps. Eyes with PCV were excluded from this study. The average age of the patients included in this study was 73.1 ± 8.8 years. A total of 45 eyes (45.5%) were included in the VMA(+) group and 54 eyes (54.5%) comprised the VMA(–) group. Patients in the VMA(–) group were older than patients in the VMA(+) group ($p = 0.020$). The baseline characteristics and the drug used according to the presence of VMA or not are shown in Table 1.

The mean number of intravitreal injections required between the third and twelfth months was 1.54 ± 1.35 for patients in the VMA(–) group and 1.69 ± 1.58 for patients in the VMA(+) group ($p = 0.79$, Mann-Whitney test).

Considering all patients, BCVA showed statistically significant improvement when the data obtained at 1, 2, and 3 months were compared with baseline. No statisti-

cally significant difference was noted when paired comparisons of BCVA between baseline, and 6 and 12 months were made for these patients (Table 2). There was no correlation between age and BCVA at baseline ($r = 0.23$; $p = 0.20$), 3 months ($r = 0.14$; $p = 0.163$), 6 months ($r = 0.18$; $p = 0.069$), and 12 months ($r = 0.935$; $p = 0.091$). The mean CRT presented a statistically significant decrease when the data obtained at 1, 2, 3, 6, and 12 months were compared with baseline (Table 3).

In the VMA(–) group, paired comparisons of BCVA showed statistically significant improvement at 1, 2, and 3 months compared to baseline. In the VMA(+) group, BCVA significantly improved only at 3 months. Compared to baseline, BCVA 6 and 12 months after treatment were not statistically different in both groups (Table 4). Paired comparisons of CRT showed statistically significant decrease 1, 2, 3, 6, and 12 months after treatment compared to baseline in the VMA(+) and VMA(–) groups (Table 5).

Table 2. BCVA of eyes diagnosed either with retinal angiomatous proliferation or typical age-related macular degeneration treated with anti-vascular endothelial growth factor agents

	BCVA (logMAR)	*p* value
Baseline	0.51±0.28 0.50 (0.30–0.70)	
1 month	0.46±0.29 0.40 (0.28–0.60)	0.019[a]
2 months	0.43±0.32 0.40 (0.20–0.50)	<0.001[b]
3 months	0.49±0.44 0.40 (0.20–0.50)	<0.001[b]
6 months	0.48±0.42 0.40 (0.20–0.70)	0.098
12 months	0.55±0.52 0.40 (0.20–0.70)	0.655

Values are presented as means ± SD followed by medians (Q1 to Q3) unless otherwise stated. BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution. Wilcoxon test. [a] $p < 0.05$ (95% CI). [b] $p < 0.01$ (99% CI).

Table 3. CRT of eyes diagnosed either with retinal angiomatous proliferation or typical age-related macular degeneration treated with anti-vascular endothelial growth factor agents

	CRT, μm	*p* value
Baseline	344.46±104.36 325.00 (267.00–396.00)	
1 month	308.90±102.94 284.00 (241.00–336.00)	<0.001[a]
2 months	301.06±101.54 272.00 (238.00–325.00)	<0.001[a]
3 months	309.52±116.40 281.00 (228.00–336.00)	<0.001[a]
6 months	305.162±102.26 286.00 (235.00–345.00)	<0.001[a]
12 months	305.90±106.89 276.00 (231.00–346.00)	<0.001[a]

Values are presented as means ± SD followed by medians (Q1 to Q3) unless otherwise stated. CRT, central retinal thickness. Wilcoxon test. [a] $p < 0.01$ (99% CI).

Discussion

The association between vitreous and retinal pathologies has been known for some time [8]. The reported incidence of VMA in patients with AMD ranges from 12.2 to 48.5% [6–9, 27]. Several previous studies have demonstrated an association between VMA and neovascular AMD, suggesting that PVD protects against neovascular AMD whereas VMA may promote this form of the disease [6–8, 27]. It is possible that persistent VMA could influence the development of neovascular AMD through the induction of chronic low-grade inflammation, prevention of diffusion of oxygen and nutrients to the macula, or confinement of proangiogenic cytokines in the macula [7, 23, 28, 29]. Nomura et al. [9], however, did not find an association between VMA and PCV. It has been suggested that the abnormal vessels in PCV usually spread beneath the RPE, possibly into the Bruch membrane, leading to less inflammatory reaction and to a smaller influence of the exudative change on the vitreomacular interface [9].

In our study, patients without VMA were older than those with VMA, which is consistent with the known increased incidence of PVD with age [30]. Most of our patients (66.3%) were women, which is in agreement with the higher prevalence of AMD among women observed in the literature [31]. It has been suggested that female gender should be considered a risk factor for PVD, possibly due to hormonal factors [32]. In the present study, women

Table 4. BCVA of eyes diagnosed either with retinal angiomatous proliferation or typical age-related macular degeneration and treated with anti-vascular endothelial growth factor agents according to the presence of VMA

	VMA(+) BCVA (logMAR)	*p* value	VMA(–) BCVA (logMAR)	*p* value
Baseline	0.49±0.29 0.50 (0.30–0.65)		0.52±0.28 0.50 (0.30–0.90)	
1 month	0.47±0.32 0.45 (0.20–0.68)	0.660	0.45±0.28 0.40 (0.30–0.60)	0.002[b]
2 months	0.45±0.38 0.40 (0.20–0.55)	0.132	0.42±0.27 0.40 (0.30–0.50)	0.002[b]
3 months	0.43±0.36 0.40 (0.20–0.60)	0.032[a]	0.44±0.35 0.40 (0.20–0.53)	0.018[a]
6 months	0.52±0.52 0.40 (0.10–0.80)	0.587	0.48±0.38 0.40 (0.20–0.70)	0.070
12 months	0.59±0.57 0.50 (0.10–0.90)	0.577	0.52±0.49 0.40 (0.20–0.70)	0.268

Values are presented as means ± SD followed by medians (Q1 to Q3) unless otherwise stated. Wilcoxon test. [a] $p < 0.05$ (95% CI). [b] $p < 0.01$ (99% CI). BCVA, best-corrected visual acuity; logMAR, logarithm of minimal angle of resolution; VMA, vitreomacular adhesion.

Table 5. CRT of eyes diagnosed either with retinal angiomatous proliferation or typical age-related macular degeneration and treated with anti-vascular endothelial growth factor agents according to the presence of VMA

	VMA(+) CRT, μm	*p* value	VMA(–) CRT, μm	*p* value
Baseline	357.62±111.22 337.00 (290.00–397.50)		333.50±97.99 302.50 (260.75–379.50)	
1 month	319.40±108.80 291.00 (257.50–333.50)	<0.001[a]	300.15±97.97 274.00 (235.50–338.25)	<0.001[a]
2 months	335.04± 106.15 285.00 (244.00–322.50)	<0.001[a]	303.89±119.91 270.00 (228.00–329.50)	<0.001[a]
3 months	323.02±112.99 289.00 (251.50–363.50)	0.002[a]	298.26±119.03 261.50 (226.75–306.50)	<0.001[a]
6 months	315.80±115.47 293.00 (233.00–369.00)	0.001[a]	296.30±89.95 282.00 (233.00–329.25)	0.001[a]
12 months	314.20±114.43 301.00 (228.50–351.00)	0.001[a]	298.98±100.74 263.50 (230.25–327.25)	0.001[a]

Values are presented as means ± SD followed by medians (Q1 to Q3) unless otherwise stated. Wilcoxon test. [a] $p < 0.01$ (99% CI). BCVA, best-corrected visual acuity; CRT, central retinal thickness; SD, standard deviation; VMA, vitreomacular adhesion.

Table 6. Review of the effects of VMA on anti-VEGF treatment

Study	Eyes, *n*	Diagnosis/ follow-up	OCT	Anti-VEGF drug	Treatment regimen	Conclusion
Lee et al. [16]	148	All AMD subtypes/ 1 year	TD-OCT	Bevacizumab or ranibizumab	PRN	VMA was associated with an inferior visual outcome
Cho et al. [17]	104	PCV/ 1 year	SD-OCT	Bevacizumab or ranibizumab	PRN	VMA was not associated with the visual outcome
Üney et al. [18]	61	All AMD subtypes/ 1 year	TD-OCT	Bevacizumab or ranibizumab	PRN	VMA was associated with an inferior visual outcome
Mayr-Sponer et al. [15]	255	All AMD subtypes/ 1 year	TD-OCT	Ranibizumab	PRN	VMA was associated with an inferior visual outcome; eyes with VMA required more injections
Nomura et al. [19]	123	All AMD subtypes/ 1 year	SD-OCT	Ranibizumab	PRN	VMA was associated with an inferior visual outcome
Waldstein et al. [20]	255	All AMD subtypes/ 1 year	TD-OCT	Ranibizumab or ranibizumab/ PDT	PRN	VMA was associated with a favorable outcome in combination therapy using PDT plus ranibizumab
Houston et al. [21]	204	All AMD subtypes/ 1 year	SD-OCT	Bevacizumab, ranibizumab, or aflibercept	Treat and extend	Eyes with VMA required more injections
Krishnan et al. [22]	63	All AMD subtypes/ 1 year	SD-OCT	Ranibizumab	PRN	VMA was associated with an inferior visual outcome
McKibbin et al. [23]	93	All AMD subtypes/ 6 months	SD-OCT	Aflibercept	PRN	VMA was not associated with visual outcome
Cuilla et al. [24]	143	All AMD subtypes/ 2 years	TD-OCT	Bevacizumab or ranibizumab	Monthly or PRN	VMA was not associated with visual outcome; eyes with VMA treated as needed required more injections

AMD, age-related macular degeneration; OCT, optical coherence tomography; PCV, polypoidal choroidal vasculopathy; PRN, pro re nata; PVD, posterior vitreous detachment; SD, spectral domain; TD, time domain; VA, visual acuity; VEGF, vascular endothelial growth factor; VMA, vitreomacular adhesion.

were older than men. Indeed, our results showed that men were more prone to presenting with VMA than women, but this result was not statistically significant. Therefore, it is possible that, in addition to hormonal factors, the more advanced age in women could explain the higher prevalence of an absence of VMA in this group of patients.

With regard to the lens status, 41.0% of the pseudophakic eyes and 48.3% of the phakic eyes presented VMA, respectively. Therefore, though not statistically significant, the presence of VMA was more common in phakic eyes, which is in accordance with the literature for such patients [33].

In the CATT study [24] it was found that current or former cigarette smokers were more likely to have VMA or vitreomacular traction, a finding that had not been previously reported. In our study, which evaluated a smaller number of eyes, there was no difference in the prevalence of VMA between smokers and nonsmokers ($p = 0.60$).

One study supported the theory that an attached posterior hyaloid may create a semipermeable barrier to molecules that cross the vitreoretinal junction, and PVD may allow increased diffusion across this junction [28]. Considering this theory, VMA may be partially responsible for a worse response to antiangiogenic therapy. Several studies have evaluated the effects of VMA on anti-VEGF treatment for neovascular AMD (Table 6). Most of them suggested that eyes with VMA had worse VA outcomes or required more intravitreal injections. However, some differences observed in the results can be partially explained by differences in their methods (e.g., different drugs, different OCT technologies, and different treatment protocols).

Just one previous paper studied the effects of VMA on anti-VEGF treatment in cases diagnosed with PCV and showed that vitreous adhesion was not associated with the visual outcome [17]. In our study, of the 27 eyes ini-

tially diagnosed with PCV, we found that 11 eyes showed extrafoveal lesions. The extrafoveal location observed in almost 41% of the eyes with PCV could certainly influence not only the vitreomacular interface but also the response to treatment. Furthermore, a recent guideline recommended that combination treatment using photodynamic therapy and anti-VEGF should be the first-line therapy for juxtafoveal and subfoveal PCV [12]. Therefore, based on all of these facts, we decided not to include eyes with this subtype of AMD in our study. All previous studies did not exclude patients diagnosed with PCV, which could have influenced the results. The prevalence of PCV ranges from 7.8 to 54.7% [34]. In a recent study, we evaluated a Brazilian cohort [35] with a predominantly Caucasian ancestry and genetic polymorphisms similar to those observed in American and European patients. Of a total of 265 evaluated eyes, 166 eyes (62.6%) were diagnosed with typical AMD, 65 (24.5%) with PCV, and 34 (12.8%) with RAP. In the present study, we found a very similar percentage. This is the first paper to evaluate the effect of VMA on the response to anti-VEGF agents, excluding eyes diagnosed with PCV.

In the present study, patients were submitted to a pro re nata therapy protocol. When the whole group of patients was evaluated, we observed that, after 3 months of treatment, there was a statistically significant improvement in BCVA. However, after 6 and 12 months, there was no statistically significant improvement in BCVA compared to baseline, in contrast to other multicenter randomized studies that used monthly protocol of treatment with anti-VEGF agents [36, 37]. Such studies had rigid inclusion and exclusion criteria for retreatment, which led to ideal treatment conditions and better long-term functional results. On the other hand, in real-life studies such this one, patients usually receive a smaller number of treatments, and consequently, experience worse functional results compared to multicenter randomized studies. Regarding the anatomic results, when we considered the whole group of patients, the mean CRT showed a statistically significant decrease when the data obtained at all visits were compared to baseline. Lee and Koh [16] and Nomura et al. [19], also published results similar to ours, showing anatomic improvement without a correspondent functional response.

When patients with and without VMA were analyzed separately, we found that their responses differed at the beginning of the treatment. Patients in the VMA(–) group achieved a statistically significant improvement in BCVA at 1, 2, and 3 months compared to baseline. For these patients, there was also an improvement in visual acuity in the sixth month, but without statistical significance (p = 0.07). In the VMA(+) group, however, this improvement was found only in the third month. Therefore, the vitreomacular interface seems to influence visual outcomes in a short-term follow-up. Indeed, in a previous study involving most of the current patients, we showed that, in a short-term follow-up (1 month), VMA was statistically associated with a worse anatomic and functional outcome than the absence of VMA [38]. In fact, the improvement occurred gradually at between 1 and 3 months in the VMA(+) group. On the other hand, in the VMA(–) group there was a conspicuous and greater response right after the first injection. For evaluation of the treatment effect, the first 3 months are essential because the greatest visual improvement occurs in this period. After the loading dose, the improvement is relatively small, and BCVA improvement depends on the treatment regimen employed. Therefore, the data obtained after the loading dose is more complex to interpret, especially in real-life studies.

It is interesting to note that the mean age of the patients in the VMA(–) group, which had better results, was higher than that in the VMA(+) group. There is no evidence in the literature that the visual outcome could be better in patients of an older age. Despite this lack of evidence, we evaluated the possible correlation between the response to treatment and the age range of all patients and found that there was no such correlation (r = 0.017 and p = 0.091, Pearson correlation test).

The literature demonstrates that there is no difference in the response to treatment of neovascular AMD with different anti-VEGF agents [24]. Even though this study was not designed to evaluate the different response between the anti-VEGF agents, the drug distribution between the VMA(+) and VMA(–) groups was similar (p = 0.06). We can thus assume that these groups were similarly affected in terms of functional and anatomical results by the use of these different drugs.

Our study was not designed to compare the numbers of injections and, as previously described, the number of treatments after the first 3 doses is heavily influenced by factors such as the ability to return to routine follow-ups and adherence to treatment.

Other long-term follow-up studies evaluating the response to anti-VEGF therapy according to the vitreomacular interface have shown that patients with VMA require more injections than patients without VMA [15, 20, 21]. It is possible that, in some cases, intravitreal injections can induce PVD and therefore favor the response to treatment, leading to a smaller number of injections. Howev-

er, we recently showed that intravitreal injections of commonly used anti-VEGF intravitreal drugs rarely induce PVD in patients with neovascular AMD. Eyes with focal VMA have a greater chance of developing PVD than eyes with a broad area of VMA [39]. In the present study, 3 eyes presented PVD during the follow-up period. Two of these patients developed PVD after their last intravitreal injection and 1 after the second injection. For a consistent evaluation of the effect of induced PVD on the visual outcome and the number of required injections, a longer follow-up period, before and after the occurrence of PVD, should be available for each of these patients.

There are some limitations in the present study. Firstly, the number of patients categorized as having RAP was small, and therefore these patients could not be analyzed separately. Secondly, as previously mentioned, the VMA(+) and VMA(–) groups comprised a relatively small number of eyes, and future studies with larger number of patients would be desirable. Furthermore, the pro re nata protocol employed in real-life studies such as this one does not allow a precise evaluation of the therapeutic response after the loading dose.

In conclusion, the results of our study indicate that posterior VMA is important to the response to treatment with anti-VEGF monotherapy. The exclusion of patients diagnosed with PCV in the present study eliminates the influence of a subset of patients with particular anatomic and pathologic characteristics that usually require a combination treatment for better results. It should be noted, however, that AMD is a multifactorial disease, and VMA is only one of the factors that could influence the course of treatment. The effect of VMA seems restricted to a short-term period, and the continuity of treatment may reduce this influence. The long-term outcome should be investigated by more strictly designed studies with a larger number of eyes included. Therefore, further controlled prospective studies are required to assess the relationship between VMA and the long-term response to anti-VEGF treatment in neovascular AMD.

Disclosure Statement

No conflict of interest exists for any of the authors. There was no financial support.

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CONCLUSÃO DO PRIMEIRO TRABALHO:

O primeiro trabalho comprovou que a AVM é importante para a resposta ao tratamento com anti-VEGF. A exclusão de pacientes diagnosticados com PCV no presente estudo eliminou a influência de um subconjunto de pacientes com características anatômicas e patológicas particulares que usualmente requerem tratamento combinado para melhores resultados. No grupo AVM (-) houve maior proporção de pacientes do sexo feminino e com idade mais avançada. Deve-se notar, entretanto, que a DMRI é doença multifatorial, e a AVM é apenas um dos fatores que poderiam influenciar o curso do tratamento. O efeito da AVM parece restrito ao curto prazo, e a continuidade do tratamento talvez possa reduzir essa influência. O resultado a longo prazo deve ser investigado por estudos mais rigorosamente concebidos com maior número de olhos inscritos. Portanto, outros estudos prospectivos controlados são necessários para avaliar a relação entre a AVM e a resposta a longo prazo ao tratamento anti-VEGF na DMRI neovascular.

OBJETIVOS DO SEGUNDO TRABALHO:

PRINCIPAL:

Avaliar a incidência de DVP induzido por injeções intravítreas de agentes anti-VEGF em pacientes com DMRI neovascular.

O segundo trabalho “Vitreomacular Interface after Anti-Vascular Endothelial Growth Factor Injections in Neovascular Age-Related Macular Degeneration” foi publicado na revista *Ophthalmology* em 2015 e encontra-se a seguir precedido pelo seu resumo em português.

RESUMO DO SEGUNDO TRABALHO:

TÍTULO: Interface vitreomacular após injeções de agentes antiangiogênicos na degeneração macular relacionada à idade forma exsudativa.

OBJETIVOS: Avaliar a incidência de descolamento do vítreo posterior (DVP) induzido por injeções intravítreas de agentes anti-fator de crescimento endotelial vascular (VEGF) em casos de degeneração macular relacionada à idade (DMRI) neovascular.

MATERIAL E MÉTODOS: Estudo de coorte, realizado em um centro único de referência. Total de 396 olhos de 295 pacientes foram diagnosticados com DMRI forma neovascular entre 2009 e 2014. Cento e vinte e cinco olhos de 112 pacientes preencheram os critérios de inclusão e foram avaliados neste estudo, que incluiu pacientes com DMRI neovascular apresentando adesão vitreomacular (AVM) detectada por tomografia de coerência óptica de domínio espectral (OCT-SD). Os olhos com AVM foram classificados de acordo com o diâmetro da ligação vítrea à superfície macular medida por OCT, com ligação de ≤1500 µm definida como focal e ligação de >1500 µm definida como ampla. Todos os pacientes receberam pelo menos 3 injeções intravítreas mensais de agentes anti-VEGF. As visitas de seguimento foram realizadas um mês após cada injeção intravítrea, com a realização da OCT-SD para avaliar a incidência de DVP.

RESULTADOS: O período médio de seguimento foi de 21,3 meses (intervalo, 3-59 meses). O número médio de injeções intravítreas foi de 8,3 (intervalo, 3-29 injeções). Os fármacos intravítreos utilizados no estudo foram ranibizumabe (51,5%), bevacizumabe (33,5%) e aflibercepte (15,0%). Sete olhos (5,6%) desenvolveram DVP após a injeção intravítrea. Cento e dezoito olhos permaneceram com AVM persistente. Os sete olhos que desenvolveram DVP foram classificados como tendo AVM focal, com o diâmetro da adesão vítrea variando de 210 µm a 1146 µm (média, 600 µm).

CONCLUSÕES: Injeções intravítreas de antiangiogênicos comumente utilizadas, raramente induzem DVP em pacientes com DMRI neovascular. Olhos com AVM focal têm maior chance de desenvolver DVP que olhos com ampla área de AVM.

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Vitreomacular Interface after Anti–Vascular Endothelial Growth Factor Injections in Neovascular Age-Related Macular Degeneration

Carlos E. Veloso, MD, PhD, Tereza M. Kanadani, MD, Frederico B. Pereira, MD, PhD, Márcio B. Nehemy, MD, PhD

Purpose: To evaluate the incidence of posterior vitreous detachment (PVD) induced by intravitreal injections of anti–vascular endothelial growth factor (VEGF) agents in cases of neovascular age-related macular degeneration (AMD).

Design: Cohort study conducted at a single tertiary referral vitreoretinal practice.

Participants: A total of 396 eyes of 295 patients were diagnosed with neovascular AMD between 2009 and 2014. A total of 125 eyes of 112 patients met the inclusion criteria and were evaluated in this study.

Methods: This study included patients with neovascular AMD who presented vitreomacular adhesion (VMA) detected by spectral-domain optical coherence tomography (OCT) at baseline. Eyes with VMA were classified according to the diameter of vitreous attachment to the macular surface measured by OCT, with attachment of $\leq$1500 μm defined as focal and attachment of >1500 μm defined as broad. All patients received at least 3 monthly intravitreal injections of anti-VEGF agents. Follow-up visits were performed 1 month after each intravitreal injection and included OCT analysis to evaluate the incidence of PVD.

Main Outcome Measures: Posterior vitreous detachment induced by anti-VEGF injections.

Results: The mean follow-up period was 21.3 months (range, 3–59 months). The mean number of intravitreal injections was 8.3 (range, 3–29 injections). Intravitreal drugs used in the study were ranibizumab (51.5%), bevacizumab (33.5%), and aflibercept (15.0%). Seven eyes (5.6%) developed PVD after intravitreal drug injection (3 eyes after the first intravitreal injection: bevacizumab in 1 and ranibizumab in 2; 2 eyes after the second injection: ranibizumab in 1 and bevacizumab in 1; 1 eye after the fourth injection: ranibizumab; and 1 eye after the sixth injection: aflibercept). A total of 118 eyes remained with persistent VMA. All 7 eyes that developed PVD were classified as having focal VMA, with the diameter of vitreous attachment ranging from 210 to 1146 μm (mean, 600 μm).

Conclusions: Intravitreal injections of commonly used anti-VEGF intravitreal drugs rarely induce PVD in patients with neovascular AMD. Eyes with focal VMA have a greater chance to develop PVD than eyes with a broad area of VMA. *Ophthalmology 2015;122:1569-1572 © 2015 by the American Academy of Ophthalmology.*

Vitreomacular adhesion (VMA) seems to play a role in the development of macular pathologies, including age-related macular degeneration (AMD).[1] Previous studies have considered persistent VMA as a possible risk factor for the development of neovascular AMD, whereas posterior vitreous detachment (PVD) seems to protect against this form of the disease.[1–4] A recent subanalysis of a randomized, double-masked, multicenter study has also shown that the configuration of the vitreomacular interface (VMI) seems to have an important effect on visual outcomes and need for re-treatment in cases of neovascular AMD. In patients with PVD, a lower treatment frequency may be feasible, whereas patients with VMA may benefit from intensive re-treatment.[5]

It is still not established whether intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors itself could induce PVD. Only 1 previous study evaluated its occurrence after intravitreal drug injection for different macular pathologies and showed that this procedure may favor the occurrence of PVD.[6] Therefore, PVD possibly induced by intravitreal injection could itself benefit the response to treatment. The purpose of this study is to evaluate the incidence of PVD induced by intravitreal injections of anti-VEGF agents in cases of neovascular AMD.

Methods

This is a prospective study designed to evaluate the incidence of PVD after intravitreal injections of currently used anti-VEGF drugs for neovascular AMD. All subjects were informed about the nature of the study and signed a written informed consent in accordance with the tenets of the Declaration of Helsinki. The ethics committees of both the Federal University of Minas Gerais and the Institute of Vision in Belo Horizonte, Brazil, approved the study. From March 2009 to December 2014, all patients with newly

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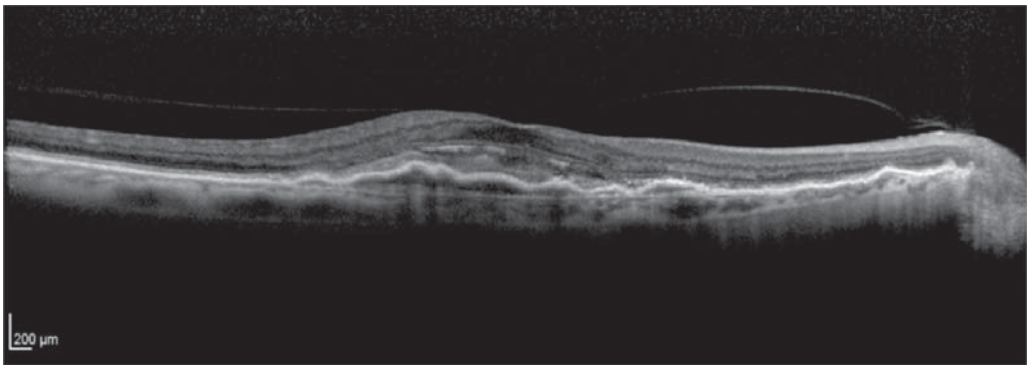

Figure 1. Example of an optical coherence tomography scan showing the presence of vitreomacular adhesion.

diagnosed neovascular AMD at the Institute of Vision were enrolled in this prospective study. At baseline, all patients underwent a complete ophthalmological examination, including biomicroscopy, retinography, fluorescein angiography, and optical coherence tomography (OCT). When indicated, indocyanine green angiography was performed for better evaluation of neovascular AMD subtypes. Spectral-domain OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) was used to evaluate the VMI. Only eyes with VMA present (Fig 1) were included in the study. Vitreomacular adhesion was defined as any adhesion of the posterior hyaloid involving the macular region (area: 8.8×5.9 mm, 30°×20°, 25-scan pattern). Patients with VMA were classified according to the diameter of vitreous attachment to the macular surface measured by OCT, with attachment of ≤1500 µm defined as focal and attachment of >1500 µm as broad. When there was no posterior hyaloid visible or when it was detected but not attached to the scanned area, we considered the vitreous to be detached. Inclusion criteria were (1) age >50 years; (2) diagnosis of neovascular AMD; (3) presence of VMA at baseline detected by OCT; (4) indication of intravitreal injection of VEGF inhibitors; and (5) follow-up of at least 3 months. Intravitreal drugs used in this study included bevacizumab (Avastin; Genentech, South San Francisco, CA), ranibizumab (Lucentis; Genentech), and aflibercept (Eylea; Regeneron Pharmaceuticals Inc., Tarrytown, NY). The injected volume of VEGF inhibitors was 0.05 ml for ranibizumab and aflibercept and 0.1 ml for bevacizumab. Exclusion criteria were (1) previous vitrectomy; (2) complicated cataract surgery; (3) concomitant inflammatory ocular conditions; (4) eyes with other conditions that are known to affect the VMI, such as retinal vascular disease, pathologic myopia, and diabetic retinopathy; (5) detectable PVD on OCT (Fig 2) or slit-lamp examination; and (6) previous intravitreal injections. All intravitreal anti-VEGF injections were performed in the operating room using an aseptic technique, including the prophylactic use of topical iodopovidone 5% before the procedures. All patients were subjected to a treatment protocol that included a loading dose with 3 intravitreal injections of anti-VEGF agents at 1-month intervals. After the third dose, patients followed a pro re nata regimen. Retreatment criteria were (1) persistence or increase of intraretinal or subretinal fluid; (2) increase of retinal pigment epithelium detachment; (3) worsening of at least 1 line of visual acuity; and (4) new subretinal hemorrhage. Follow-up visits, including OCT, were schedule to be performed 1 month after each intravitreal injection. Optical coherence tomography was performed and its data were analyzed separately by 3 retinal specialists (C.E.V., T.M.K., F.B.P.). Each retinal physician was blinded to the classifications determined by the others. If there was any disagreement, they evaluated the data simultaneously and came to a consensus. All intravitreal injections were performed by a single retinal specialist (M.B.N.).

Results

A total of 396 eyes of 295 patients were diagnosed with neovascular AMD. From this total, 166 eyes (41.9%) presented with VMA. A total of 125 eyes of 112 patients met the inclusion criteria and were evaluated in this study. The mean age was 70.6 years (range, 52−84 years), and 62 patients (55.4%) were female. A total of 68 eyes (54.4%) were phakic, and 57 eyes (45.6%) were pseudophakic. The mean follow-up period was 21.3 months (range, 3−59 months). The mean number of intravitreal injections was 8.3 (range, 3−29 injections). Patients who developed PVD required a mean of 7.9 injections, and patients with persistent VMA required a mean of 8.3 injections. Intravitreal drugs used in the study were ranibizumab (51.5%), bevacizumab (33.5%), and aflibercept (15.0%). Seven eyes (5.6%) developed PVD after intravitreal drug injection (3 eyes after the first intravitreal

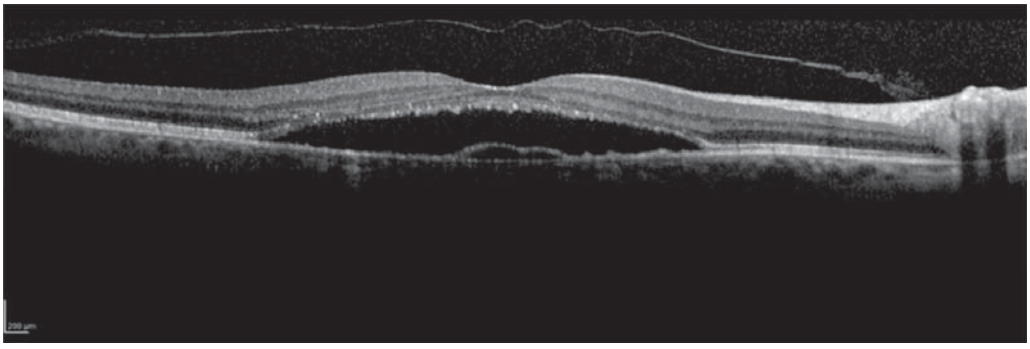

Figure 2. Example of optical coherence tomography scan showing posterior vitreous detachment.

injection: bevacizumab in 1 and ranibizumab in 2; 2 eyes after the second injection: ranibizumab in 1 and bevacizumab in 1; 1 eye after the fourth and last injection: ranibizumab; 1 eye after the sixth and last injection: aflibercept). A total of 118 eyes remained with persistent VMA. Patients who developed PVD had the following ages: 78, 56, 77, 75, 63, 61, and 66 years. Three of those eyes were phakic, and 4 were pseudophakic. Of the total of 125 eyes included in the study, 25 (20.0%) had the diagnosis of polypoidal choroidal vasculopathy, 11 (8.8%) had the diagnosis of retinal angiomatous proliferation, and 89 (71.2%) had the diagnosis of typical AMD. All eyes that developed PVD after intravitreal anti-VEGF injection were typical AMD cases. Of the total of 125 eyes, 10 were classified as having focal VMA and 115 showed broad VMA. All 7 eyes that developed PVD were classified as having focal VMA, with the diameter of vitreous attachment ranging from 210 to 1146 μm (mean, 600 μm).

Discussion

Several previous studies have suggested an association between VMA and neovascular AMD, suggesting that PVD may protect against neovascular AMD, whereas VMA may promote this form of the disease.[1–4] These reports pointed to higher rates of VMA and lower rates of PVD in eyes with neovascular AMD compared with eyes with dry AMD or no disease. The reported incidence of VMA in the literature ranges from 12.2% to 48.5%.[1–4,7–9] In our study, 166 eyes (41.9%) presented VMA. It is possible that persistent VMA influences the development of choroidal neovascularization through induction of chronic low-grade inflammation, prevention of diffusion of oxygen and nutrients to the macula, or confinement of proangiogenic cytokines in the macula.[4,10,11]

Vitreomacular adhesion also may explain the poor response to anti-VEGF treatment for choroidal neovascularization in some cases. A recent study supported the theory that an attached posterior hyaloid may create a semipermeable barrier to molecules that cross the vitreoretinal junction, and a PVD may allow for increased diffusion across this junction.[12] On the basis of this theory, it seems that VMA may be partially responsible for a worse response to anti-VEGF therapy.[4,5] Therefore, PVD possibly induced by intravitreal injections of drugs commonly used to treat AMD could favor the outcome.

The purpose of our study was to investigate whether intravitreal injection induces PVD in eyes with neovascular AMD. Only 1 previous study evaluated the occurrence of PVD after intravitreal drug injection for different macular pathologies and showed that this procedure may lead to PVD. Geck et al[6] prospectively evaluated 61 eyes within a mean follow-up period of only 11.1 weeks. They showed that 15 eyes (24.6%) developed a PVD after intravitreal injection (n = 6 after ranibizumab, n = 7 after bevacizumab, and n = 2 after triamcinolone). They also performed spectral-domain OCT (Cirrus-OCT; Zeiss, Jena, Germany) to better analyze the presence of VMA.[6] Unlike this only previously published study, our findings showed that intravitreal injection of anti-VEGF agents rarely induces PVD. The study conducted by Geck et al involved a mixture of different underlying diseases (neovascular AMD, diabetic macular edema, macular edema secondary to retinal vein occlusions, and cystoid macular edema due to cataract surgery or uveitis).[6] These different clinical entities might themselves have an influence on the development of PVD because inflammation or recent cataract extraction may promote hyaloid detachment.

In this study, 3 eyes developed PVD after the first intravitreal injection, 2 eyes developed PVD after the second injection, 1 eye developed PVD after the fourth and last injection, and 1 eye developed PVD after the sixth and last injection. For a consistent evaluation of the effect of induced PVD on the visual outcome and the number of required injections, a longer follow-up period before and after the occurrence of PVD should be available for each of these patients. In addition, the small number of eyes that developed PVD in our study does not allow a reliable statistical analysis. Therefore, we could not evaluate the effect of the induced PVD on the response to treatment. Posterior vitreous detachment could occur spontaneously because of the natural history and not necessarily be related to the injections. However, the fact that all 7 eyes developed PVD within a relatively short period after intravitreal injections indicates that, rather than being coincidental, PVD in these cases might have been induced by the intravitreal injections. It is not clear whether PVD occurred as the result of a pharmacologic or mechanical effect of the injection.

A previous multicenter, randomized, double-blind study involving patients with vitreomacular traction and macular holes demonstrated that 10.1% of the eyes treated with a placebo injection (0.10 ml volume) showed resolution of VMA 28 days after the procedure, suggesting that the mechanical effect of the injection may be relevant.[13] It is important to note that, in that study, all treated patients had focal macular adhesion, defined as vitreous adhesion to the macula within a 6-mm central retinal field. By contrast, our study included eyes with focal VMA (<1500 μm) and broad vitreous adhesion, and the overall incidence of vitreous release after injections was only 5.6%. However, if we considered only eyes with focal VMA, the incidence would be higher (7/10 eyes). These differences could be explained by differences between the 2 studies, including different diseases, different criteria to define focal VMA, and multiple injections and a longer follow-up period in our study. The 1500-μm cutoff has been selected in this study for several reasons. The 1500-μm diameter is a known area of increased vitreous adhesion to the fovea. In addition, it has been used routinely to distinguish focal from broad VMA in the published vitreoretinal literature and at most OCT reading centers.[13,14] Moreover, it was also the basis for the recent classification used by the International Vitreomacular Traction Study Group.[15]

Study Limitations

It would be reasonable to expect that a greater injected volume could be associated with a higher proportion of induced PVD cases. However, only 2 eyes that developed PVD were submitted to 0.1 ml bevacizumab. A limitation of our study was the lack of an age-matched control group, which led us to compare our findings with published data.[6] John et al[16] recently evaluated 106 eyes of 81 patients with idiopathic VMA who were followed for a mean period of 23

months. By the last follow-up visit, spontaneous release of VMA occurred in 34 of those eyes (32%), a significantly higher incidence compared with ours. It is important to note that idiopathic VMA cases are more prone to imminent PVD because there is usually a smaller area of vitreous attachment in such eyes. However, the majority of our cases presented a broad VMA, and only patients with focal VMA developed PVD after anti-VEGF injections.

In conclusion, our study suggests that focal VMA is a significant factor for PVD, but when all eyes with VMA (broad and focal) were evaluated, it was observed that injections of commonly used intravitreal anti-VEGF drugs rarely induced PVD in patients with neovascular AMD.

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Footnotes and Financial Disclosures

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Data acquisition and/or research execution: Veloso, Kanadani, Pereira, Nehemy

Data analysis and/or interpretation: Veloso, Kanadani, Pereira, Nehemy

Manuscript preparation: Veloso, Kanadani, Pereira, Nehemy

Abbreviations and Acronyms:
AMD = age-related macular degeneration; **OCT** = optical coherence tomography; **PVD** = posterior vitreous detachment; **VEGF** = vascular endothelial growth factor; **VMA** = vitreomacular adhesion; **VMI** = vitreomacular interface.

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CONCLUSÃO DO SEGUNDO TRABALHO:

O segundo estudo demonstrou que a AVM focal é fator significativo para DVP mas, quando todos os olhos com AVM (ampla e focal) foram avaliados, observou-se que as injeções intravítreas de drogas anti-VEGF, raramente, induziram DVP em pacientes com DMRI neovascular.

O DVP pode ocorrer espontaneamente por causa da história natural e não necessariamente estar relacionado às injeções. No entanto, o fato de todos os sete olhos terem desenvolvido DVP em um período relativamente curto após injeções intravítreas, indica que, em vez de coincidência, o DVP nesses casos pode ter sido induzido pelas injeções intravítreas. Não está claro se o DVP ocorreu como resultado de efeito farmacológico ou mecânico da injeção.

OBJETIVOS DO TERCEIRO TRABALHO:

PRINCIPAIS:

- Avaliar a espessura subfoveal da coroide (ESC) e o efeito do tratamento antiangiogênico nos subtipos de DMRI neovascular;

- Identificar eventual correlação entre a ESC e o número de injeções;

- Avaliar a correlação entre a ESC e a acuidade visual em todos os pacientes da amostra e entre os subtipos.

O terceiro trabalho “Subfoveal choroidal thickness in eyes with neovascular age-related macular degeneration treated with anti-vascular endothelial growth factor agents” foi submetido, em julho de 2017, à revista *Ophthalmologica* e encontra-se a seguir precedido pelo seu resumo em português.

RESUMO DO TERCEIRO TRABALHO:

TÍTULO: Espessura subfoveal da coroide em olhos com degeneração macular relacionada à idade (DMRI) forma neovascular tratados com agentes anti-fator de crescimento endotelial vascular (VEGF).

OBJETIVO**:** Avaliar a espessura subfoveal da coróide (ESC) e o efeito do tratamento com agentes anti-VEGF nos subtipos de DMRI neovascular.

MATERIAL E MÉTODOS: Foram estudados 128 olhos de 107 pacientes com DMRI neovascular. Avaliou-se prospectivamente a acuidade visual (AV) e a ESC no *baseline*, três, seis e doze meses após o tratamento com agentes anti-VEGF. Os pacientes foram subdivididos nos subtipos DMRI típica, vasculopatia polipoidal da coroide (PCV) e proliferação angiomatosa da retina (RAP).

RESULTADOS: dos 107 pacientes, 60 eram do sexo feminino e 47 eram do sexo masculino; a média de idade foi de 73,6 ± 8,9 anos. Oitenta e cinco (66,4%), 31 (24,2%) e 12 (9,4%) olhos foram atribuídos aos subtipos típica, PCV e RAP, respectivamente. A média da AV no *baseline* foi 0,75 ± 0,26, 0,72 ± 0,21 e 0,77 ± 0,24 logMAR nos subtipos típica, PCV e RAP, respectivamente (p = 0,774). A média da ESC no *baseline* foi 203,20 µm ± 35,80 µm, 271,80 µm ± 24,50 µm e 182,93 µm ± 31,31 µm nos subtipos típica, PCV e RAP, respectivamente (p <0,001). A média de ESC diminuiu significativamente desde o *baseline* até três, seis e doze meses após o tratamento. O subtipo RAP apresentou diminuição significativamente maior na ESC em comparação aos outros subtipos (p = 0,01). Não houve correlação entre a redução percentual da ESC e o número de injeções (r = - 0,02; p = 0,823). Não houve associação entre a ESC basal e a acuidade visual final aos 12 meses (r = 0,0; p = 0,586).

CONCLUSÕES: A ESC foi maior nos olhos com PCV e menor nos olhos com RAP. A redução na ESC após o tratamento foi maior nos casos de RAP. A diminuição da ESC após doze meses de tratamento anti-VEGF não foi associada ao número de injeções e não houve correlação entre a ESC basal e a acuidade visual final em todos os subtipos de DMRI.

Subfoveal choroidal thickness in eyes with neovascular age-related macular degeneration treated with anti-vascular endothelial growth factor agents

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Running head: SFChT after therapy in neovascular AMD.

Key words: AMD, anti-VEGF treatment, Subfoveal choroidal thickness.

Summary statement: No previous studies have evaluated the relationship between SFChT and visual outcome in AMD subtypes. In the present study, we aimed to examine the change in SFChT after treatment in various AMD subtypes, and to assess the relation between such changes after treatment and visual outcome over a 12-month follow-up period using EDI-OCT.

Abstract

Purpose: We aimed to assess the subfoveal choroidal thickness (SFChT) and the effect of treatment with anti-vascular endothelial growth factor (VEGF) agents on the SFChT in age-related macular degeneration (AMD) subtypes.

Methods: We enrolled 128 eyes of 107 patients with neovascular AMD (60 women; 47 men; mean age, 73.6 ± 8.9 years), and prospectively evaluated the best-corrected visual acuity (BCVA) and SFChT at baseline, and 3, 6 and 12 months after treatment with anti-VEGF agents. Patients were assigned to the typical AMD, polypoidal choroidal vasculopathy (PCV), and retinal angiomatous proliferation (RAP) subgroups.

Results: In total, 85 (66.4%), 31 (24.2%), and 12 (9.4%) eyes were assigned to the typical AMD, PCV, and RAP subgroups, respectively. The baseline mean BCVA was 0.75 ± 0.26, 0.72 ± 0.21, and 0.77 ± 0.24 logMAR in the typical AMD, PCV, and RAP subgroups, respectively (p=0.774). The baseline mean SFChT was 203.20 ± 35.80, 271.80 ± 24.50, and 182.93 ± 31.31 μm in the typical AMD, PCV, and RAP subgroups, respectively (p<0.001). Mean SFChT significantly decreased from baseline to 3, 6, and 12 months after treatment. The RAP subtype presented a significantly higher decrease in SFChT as compared to the other subtypes (p=0.01). The percentage reduction in SFChT was not significantly correlated with the number of injections (r=-0.02; p=0.823). No association was observed between baseline SFChT and final visual acuity at 12 months (r=0.0; p=0.586).

Conclusions: SFChT was greatest in eyes with PCV and least in eyes with RAP. The reduction in SFChT after treatment was greater in the RAP cases. The decrease in SFChT after 12 months of anti-VEGF treatment was not associated with the number of injections and there was no correlation between the baseline SFChT and visual acuity in all AMD subtypes.

Introduction

Age-related macular degeneration (AMD) is associated with significant visual morbidity, and is the leading cause of irreversible blindness in the developed world.[1] The pathogenesis and risk factors for the development of AMD remain unclear.[2] The introduction of indocyanine green (ICG) angiography has enabled better visualization of choroidal circulation, and thus, neovascular AMD has become recognized as a broad spectrum of diseases that includes distinctive subtypes such as polypoidal choroidal vasculopathy (PCV) and retinal angiomatous proliferation (RAP). Further advancements in spectral domain optical coherence tomography (SD-OCT) has facilitated cross-sectional imaging of the retina with adequate resolution, which has consequently improved our understanding of these AMD subtypes.[3-5] Detailed imaging of the choroidal cross-section has also been recently achieved through the use of the Heidelberg Spectralis^{TM} SD-OCT device with enhanced depth imaging (EDI).[6] In cases of neovascular AMD, the measurement of choroidal thickness with this method appear to be important not only for diagnosis, but also for the evaluation of therapeutic intervention.[7-12] Recently, new versions of other OCT's equipment have also been able to perform such measurements. Patients with AMD reportedly have a reduced choroidal thickness as compared to age-matched normal controls. [13,14] Furthermore, different AMD subtypes have distinct characteristics. Recently, some researchers have reported that the subfoveal choroidal thickness (SFChT) is greater in eyes with PCV than in eyes with typical AMD.[15,16] Moreover, eyes with RAP had a significantly thinner subfoveal choroid as compared to normal eyes, and the morphologic features in these cases might be related to the pathologic mechanism of RAP.[17] Some

studies have evaluated the choroidal thickness after anti-vascular endothelial growth factor (VEGF) treatment, but have indicated controversial results.[7,9,11,12,18,19,20,21,22] Additionally, SFChT was recently found to be a predictive factor for visual outcome and treatment response in typical neovascular AMD.[18] To our knowledge, no previous studies have evaluated the relationship between SFChT and visual outcome in different AMD subtypes. Hence, in the present study, we aimed to examine the change in SFChT after treatment in various AMD subtypes, and to assess the relation between such changes after treatment and visual outcome over a 12-month follow-up period using EDI-OCT.

Methods

Study design

All the subjects of this prospective study were informed of the nature of the study and they provided consent, and the research adhered to the tenets of the Declaration of Helsinki. The ethics committees of both the Institute of Vision and the Federal University of Minas Gerais in Belo Horizonte, Brazil, have approved the study.

Patients

We considered patients who were diagnosed with AMD from June 2012 to August 2015 at the Institute of Vision, and who underwent a complete ophthalmologic examination, including slit-lamp biomicroscopy, color fundus photography, fluorescein angiography, and OCT. Indocyanine green angiography was performed when neovascular AMD subtypes (PCV and RAP) were suspected. The inclusion criteria were as follows: age ≥ 50 years;

diagnosis of active neovascular AMD; indication for treatment with anti-VEGF agents in either eye, follow-up for a minimum of 12 months; and visual acuity ≥ 20/400. The exclusion criteria were as follows: cicatricial AMD, choroidal neovascularization secondary to any cause, except for AMD; concomitant inflammatory ocular disease; eyes that had undergone vitrectomy or photodynamic therapy; and other ocular conditions that might affect visual acuity.

The diagnostic criteria for PCV were based on a previous study, and diagnosis was made based on data from fundus examinations, ICG angiography [23], and FA and SD-OCT examinations. Definite cases of PCV exhibited early subretinal focal ICG angiogram hyperfluorescence (i.e., hyperfluorescence that appeared within the first 6 min after ICG injection) and at least one of the following angiographic or clinical findings: hyperfluorescence associated with a branching vascular network; presence of a pulsatile polyp; a nodular appearance in the stereoscopic view; presence of a hypofluorescent halo in the first 6 min; presence of orange subretinal nodules in the stereoscopic color fundus photograph; and hyperfluorescence associated with massive submacular hemorrhage (defined as hemorrhage of at least 4 disk areas). The diagnostic criteria for RAP were based on a previous study and included data from the fundus examination, FA and ICG angiography, as well as from SD-OCT. [24] Definite cases should have the following findings: preretinal, intraretinal, or subretinal hemorrhage; intraretinal edema; presence of retinal dilated perfusing arterioles or draining venules or the presence of serous epithelial detachment and presence of focal ICG angiogram hyperfluorescence (i.e., “hot spot”), retinal-retinal anastomosis, or retinal-choroidal anastomosis. Patients with

neovascular AMD without signs that would lead to a diagnosis of PCV or RAP were diagnosed with typical AMD.

Anti-VEGF treatment

Intravitreal anti-VEGF injections were performed using bevacizumab (1.25 mg/0.05 ml; Avastin®, Genentech Inc.), ranibizumab (0.5 mg/0.05 mL; Lucentis®, Genentech Inc.), or aflibercept (40 mg/ml; Eylea®, Bayer). All intravitreal anti-VEGF injections were performed in the operating room by a single retinal specialist with an aseptic technique; prophylaxis with 5% topical iodopovidone was ensured. All the patients were treated in accordance with a protocol that included a loading dose with 3 intravitreal injections at 1-month intervals. After the third dose, the patients followed a *pro re nata* regimen, with monthly visits. Retreatment criteria were as follows: persistence of or increase in intra- or subretinal fluid; increase of retinal pigment epithelial detachment; worsening of at least one line of VA; and new subretinal hemorrhage. Furthermore, after the first injection, there was a possibility of exchange of the intravitreous drug.

Measurement of SFChT using EDI-OCT

Optical coherence tomography images were obtained using a 20 B-scans horizontal raster protocol and 9-mm vertical and horizontal linear scans in EDI mode. All 20 B-scans were acquired in a continuous, automated sequence, and covered a 30º × 15º area of the macula. Each scan was 9.0 mm in length, and was spaced 240 μm apart from each other. To determine the SFChT, the vertical distance was measured manually at the fovea, from the hyperreflective

line of Bruch's membrane to the hyperreflective line of the chorioscleral interface, by using the caliper tool of the OCT Heidelberg Eye Explorer software (Heidelberg Engineering). The SFChT was measured at baseline, and at 3, 6 and 12 months after the initial anti-VEGF treatment. Certified OCT technicians acquired the OCT scans, and 3 retinal specialists (TCK, CEV and MBN) analyzed the results.

Visual acuity measurement

Best-corrected visual acuity (BCVA) was measured at baseline and at 1, 2, 3, 6, and 12 months after the initial anti-VEGF treatment. The BCVA was determined by a masked physician using a Snellen chart, and was then converted to the logarithm of the minimal angle of resolution (logMAR) value. [25]

Statistical analysis

All variables were tested for normal distribution using the Kolmogorov–Smirnov test. Categorical variables were compared using the Fisher's exact test. To assess the magnitude and direction of the association between SFChT and BCVA at baseline and at 3, 6, and 12 months after treatment, the Pearson correlation test was used. Contingency tables were used to assess the association between the number of injections and the type of drug in each subgroup. Pearson's chi-square test was adopted to test the statistical significance of the association between these variables. The Kruskal-Wallis test was used to compare the SFChT (throughout the study period) with the number of injections. The survey data were processed in the statistical program Predictive Analytics Software (PASW 18). Statistically significant associations were considered at a p value of <0.05.

Results

Baseline characteristics

In total, 128 eyes from 107 patients (60 women and 47 men; mean age, 73.6 ± 8.9 years) with a diagnosis of neovascular AMD were included. After FA, ICG, and OCT analysis, the eyes with neovascular AMD were categorized into 3 subgroups: 85 (66.4%), 31 (24.2%), and 12 (9.4%) eyes were assigned to the typical AMD, PCV, and RAP subgroups, respectively. The mean age of patients in typical AMD, PCV, and RAP subgroups was 72.9 ± 9.5, 73.5 ± 7.6, and 78.5 ± 5.7 years, respectively; although patients with RAP were older, the ages did not significantly differ among the subgroups (p=0.121). The mean baseline BCVA in the typical AMD, PCV, and RAP subgroups was 0.75 ± 0.26, 0.72 ± 0.21, and 0.77 ± 0.24 logMAR, respectively, and the value did not significantly differ among the groups (p=0.774). The mean baseline SFChT in the typical AMD, PCV, and RAP subgroups was 203.20 ± 35.80, 271.80 ± 24.50, and 182.93 ± 31.31 μm, respectively; this value significantly differed among the groups (p<0.001), and was greatest in the PCV group and least in the RAP group. No significant correlation (p≥0.05) was observed between the baseline SFChT value and patient age. The mean number of intravitreal injections performed during the study was 4.7 ± 1.8 overall, but was 4.9 ± 1.6, 5.0 ± 1.6, and 4.9 ± 1.5 in the in typical AMD, RAP, and PCV subgroups, respectively; this value did not significantly differ between the groups.

Visual acuity and optical coherence tomography outcomes

All subtypes

When all the patients were considered, the BCVA indicated a significant improvement from baseline to 1, 2, 3 and 6 months and no statistically significant difference was noted when BCVA was analyzed between baseline and 12 months after treatment. When BCVA was analyzed between months 1, 2, 3, 6 and 12 (post-hoc test) no statistically significant difference was noted. The mean SFChT significantly decreased from baseline to 3, 6, and 12 months after treatment (Table 1). The Pearson´s correlation test showed that a better BCVA at baseline was associated with a better BCVA at the end of the treatment; this correlation was considered very strong ($r=0.70$; $p<0.001$). The Pearson´s correlation test also demonstrated a positive association between the visual acuity at 12 months after treatment and the number of injections performed, although this association was not significant ($r=-0.16$; $p=0.076$). No association was observed between the BCVA measured at 12 months after treatment and baseline SFChT ($r=0.0$; $p=0.586$). The SFChT measured at 12 months after treatment was significantly associated with the baseline SFChT ($r=0,98$; $p<0.001$). Furthermore, the Pearson correlation test did not show any significant correlation between the number of injections and the percentage of SFChT reduction ($r=-0.02$; $p=0.823$). No correlation was also observed between patient age and SFChT reduction ($r=-0.05$; $p=0.622$).

AMD subtypes

There was no significant difference ($p\geq0.05$) among the 3 subtypes in terms of BCVA at baseline and at other visits. For all the subtypes, there was a significant reduction on the percentage of the SFChT when comparing baseline and 12 months ($p< 0.05$; Figure 1). The RAP subtype demonstrated a more significant decrease, while the typical and PCV subtypes difference was not

statistically significant (Table 2). When considering all the patients and subtypes, the magnitude of correlation between the change in BCVA and the percentage of SFChT reduction over time was calculated and found to be practically null, which means that there was no relationship between these 2 variables ($p>0.05$) either for all subtypes or for each of them separately (Figure 2).

Discussion

The choroidal structure is of particular interest in AMD because the abnormalities of choroidal circulation have been hypothesized to contribute to AMD development.[26] Some studies suggest that AMD might be a vascular disease, wherein inadequate choroidal perfusion leads to hypoxia and ischemia of the retinal pigment epithelium along with the subsequent production of VEGF, which ultimately results in choroidal neovascularization.[27,28]The choroid is known to have a dynamic role in the pathogenesis of AMD, and a few previous studies have examined the thickness of the choroid in different AMD subtypes and the influence of anti-VEGF treatment on the SFChT. Our study was designed to evaluate the change in choroidal thickness and the relationship between the SFChT and the change in visual acuity after treatment with anti-VEGF agents in all AMD subtypes.

In the present study, eyes with neovascular AMD were categorized into 3 subgroups: 66.4%, 24.2%, and 9.4% were diagnosed with typical AMD, PCV, and RAP, respectively, which is representative of characteristics of AMD patients of Caucasian origin evaluated by ICG angiography.[29] It has been suggested that RAP is more prevalent in older patients, whereas PCV predominantly occurs in middle-aged to elderly subjects, most commonly

affecting patients in their 50s or 60s.[30,31] In the present study, the mean age of patients diagnosed with RAP was higher, although this difference was not statistically significant.

We did not observe any significant difference ($p \geq 0.05$) among the 3 subtypes in terms of the BCVA value at baseline. The BCVA slightly increased at 1 month and then stabilized at all subsequent visits, and no significant difference was observed between the groups at any time-point. It is known that randomized clinical trials present better visual outcomes than real-life studies, such as the present one. [32,33] There are many reasons for such differences, including the selection of patients for treatment and the number of visits and retreatments; although the analysis of this difference is important, the discussion on this topic is beyond the scope of the present study. In this study, we found that the baseline BCVA was the most important factor correlated with a better BCVA at 12 months after treatment. This finding is consistent with the results of previous studies, which analyzed the baseline characteristics with predictive value for visual prognosis and treatment frequency in ranibizumab-treated patients with wet AMD. The baseline predictors of visual acuity 20/40 or better, at 12 months, included better baseline BCVA, smaller total choroidal neovascularization leakage area, and presence of subretinal fluid. [34]

A previous study performed EDI in eyes with PCV and typical neovascular AMD, and compared them to age-matched controls. They found a significantly greater SFChT in eyes with PCV (438.3±87.8 μm, $p<0.001$), and reduced SFChT in eyes with typical AMD (171.2±38.5 μm, $p=0.004$), as compared to age-matched controls. The authors further proposed that choroidal thickness, as imaged by EDI-OCT, might be a useful diagnostic marker for differentiating

PCV from typical AMD.[35] In the present study, we found that, at baseline, patients diagnosed with PCV had the greatest SFChT, whereas patients with RAP had the least SFChT. These findings are in agreement with the previously published data. [8,9,15,16,17] It is possible that the thin choroid is related to the pathologic mechanism of RAP. However, the precise reason for reduced choroidal thickness in such patients remains unclear.

No significant correlation was observed between the SFChT and patient age in the present study. It is possible that the relatively narrow ranges of age distribution in this study led to a failure in detecting an existing correlation.

The results of our study demonstrated a reduction in OCT choroidal measurements among patients diagnosed with AMD and treated with anti-VEGF agents during a 1-year follow-up period. The present study showed that the percentage of SFChT reduction was higher in the RAP group, when compared to the other subtypes. Several studies have evaluated the influence of anti-VEGF treatment on the SFChT in patients with AMD, and have reported controversial results. [7,9,11,12,18,19,20,21,22] In the present study, we evaluated all the AMD subtypes and employed 3 types of anti-VEGF agents using a *pro re nata* regimen, and observed a reduction in the SFChT among patients with all AMD subtypes treated with anti-VEGF agents after 12 months. Although the reduction was numerically similar between the 3 subtypes, the percentage of reduction in the RAP group was higher than that in PCV and typical subtypes. This can be explained by the fact that patients with RAP usually present with a reduced SFChT at baseline.

There are 2 possible hypotheses to explain the decrease in SFChT observed in this study. Patients with neovascular AMD might experience accelerated

choroidal thinning due to vascular or metabolic factors, which might contribute to the pathogenesis of AMD. Another possibility is that the treatment for neovascular AMD with intravitreal anti-VEGF agents might decrease the SFChT. VEGF is expressed in the retinal pigment epithelium of normal eyes, where it is thought to be a trophic factor for the choriocapillaris and considered to play a role in choriocapillaris survival and permeability. VEGF-A is a glycoprotein that is believed to have an important role in the regulation of the choroidal vasculature. [36-38] Therefore, continuous VEGF blockage with anti-VEGF agents in the treatment of neovascular AMD could negatively affect the maintenance of the choroid. Clinically, it has been demonstrated that retinal pigment epithelial cells undergo progressive atrophy in neovascular AMD patients undergoing treatment with intravitreal anti-VEGF therapy, although it is unclear whether this change is related to anti-VEGF treatment or a consequence of the natural history of the disease. [36]

The relationship between SFChT and visual outcome in neovascular AMD was recently reported by Kang *et al*. They suggested that the baseline SFChT might be a predictive factor for the visual outcome and treatment response in typical exudative AMD after intravitreal ranibizumab injections during a 6-month follow-up period. The authors believed that patients with a relatively thicker choroid at baseline might have more choroidal blood supply and a larger choriocapillaris, which might have led to a greater potential for recovery after treatment. In addition, reduced choroidal thickness in AMD patients might represent a more prolonged and/or severe disease status, which could limit the treatment efficacy. [18] In contrast, the present study found no correlation between the baseline SFChT and visual acuity in all AMD subtypes. To our knowledge, this

is the first study to analyze the relationship between SFChT and visual acuity in each of the AMD subtypes.

Our study showed no relationship between the number of intravitreal anti-VEGF injections and the reduction of SFChT in the eyes of patients with neovascular AMD. This is in agreement with the findings of Rahman *et al*. who obtained similar results in a small case series of 15 patients. [39] Nevertheless, this result should be interpreted with care, as the number of injections between 3 and 12 months was generally low, similar to that in other real-life studies. [40]

The present study has certain limitations. The number of patients enrolled in all AMD subtypes was unequal and relatively low in the RAP and PCV groups, which prevents a more reliable analysis of the data. The lack of a control group for comparison to assess the real effect of anti-VEGF treatment on SFChT measurements is another limitation of this manuscript.

In conclusion, this study found that there is no correlation between baseline SFChT and final visual acuity at 12 months. Furthermore, this study also showed that there is a decrease in the SFChT in all AMD subtypes treated with anti-VEGF over a 12-month follow-up period. A higher percentage of reduction in SFChT was observed in patients diagnosed with RAP. It is unclear whether this decrease represents the natural history of the different AMD subtypes, or whether it is related to treatment with anti-VEGF agents.

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Title:	Subfoveal choroidal thickness in eyes with neovascular age-related macular degeneration treated with anti-vascular endothelial growth factor agents
Authors(s):	TEREZA KANADANI (Author), CARLOS VELOSO (Co-author), MARCIO NEHEMY (Co-author)
Keywords:	Age-related macular degeneration (AMD/ARMD), Anti-VEGF (vascular endothelial growth factor), SUBFOVEAL CHOROIDAL THICKNESS
Type:	Research Article

Table 1: Best-corrected visual acuity and subfoveal choroidal thickness in all patients with AMD treated with anti-vascular endothelial growth factor agents over 12 months of follow-up compared with baseline.

	BCVA - Mean ± SD (logMAR)	p-value	SFChT- Mean ± SD (µm)	p-value
Baseline	0.61 ± 0.38		216.4 ± 44.9	
1 month	0.53 ± 0.38	**P<0.001****		
2 months	0.52 ± 0.43	**P<0.001****		
3 months	0.52 ± 0.44	**P<0.001****	210.7 ± 44.1	**p<0.001****
6 months	0.54 ± 0.46	**0.017***	204.5 ± 44.7	**p<0.001****
12 months	0.57 ± 0.48	0.524	198.0 ± 44.6	**p<0.001****

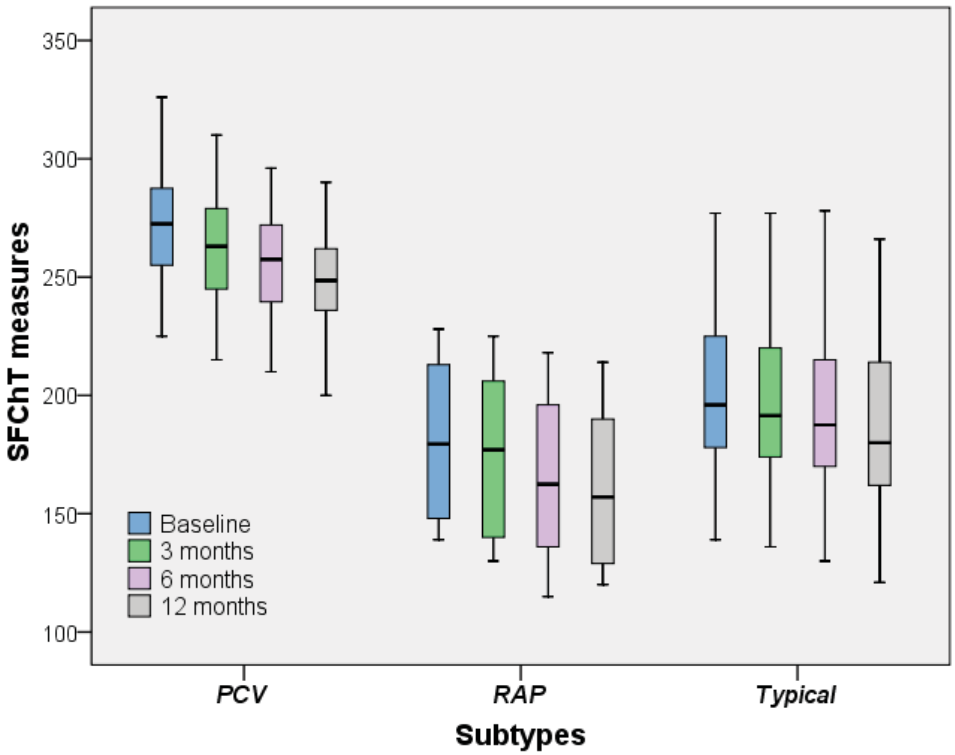
Post-hoc's test
p-value < 0.01** (confidence interval= 99%); p-value< 0.05 * (confidence interval= 95%)
BCVA: Best-Corrected Visual Acuity
SFChT: Subfoveal Choroidal Thickness
AMD: neovascular age-related macular degeneration

Table 2: Comparison of subfoveal choroidal thickness reduction over the 12-month follow-up period among the 3 neovascular age-related macular degeneration subtypes.

Subtype	N	% SFChT reduction				p value
		Min	Max	Mean	SD	
PCV	31	0.4	14.0	8.3	3.3	**0.010** RAP>(PCV=TYPICAL)
RAP	12	5.1	19.0	12.1	4.5	
TYPICAL	85	-2.7	20.9	8.4	4.4	
ALL PATIENTS	128	-2.7	20.9	8.8	4.3	

Note: *% SFChT reduction*= (1–baseline SFChT/SFChT at 12 mo) ×100

SFChT: subfoveal choroidal thickness, PCV: polypoidal choroidal vasculopathy, RAP: retinal angiomatous proliferation, N: number of patients, SD: standard deviation, Min: minimum, Max: maximum.


350
300
250
200
150
100
SFChT measures
Baseline
3 months
6 months
12 months
PCV
RAP
Typical
Subtypes

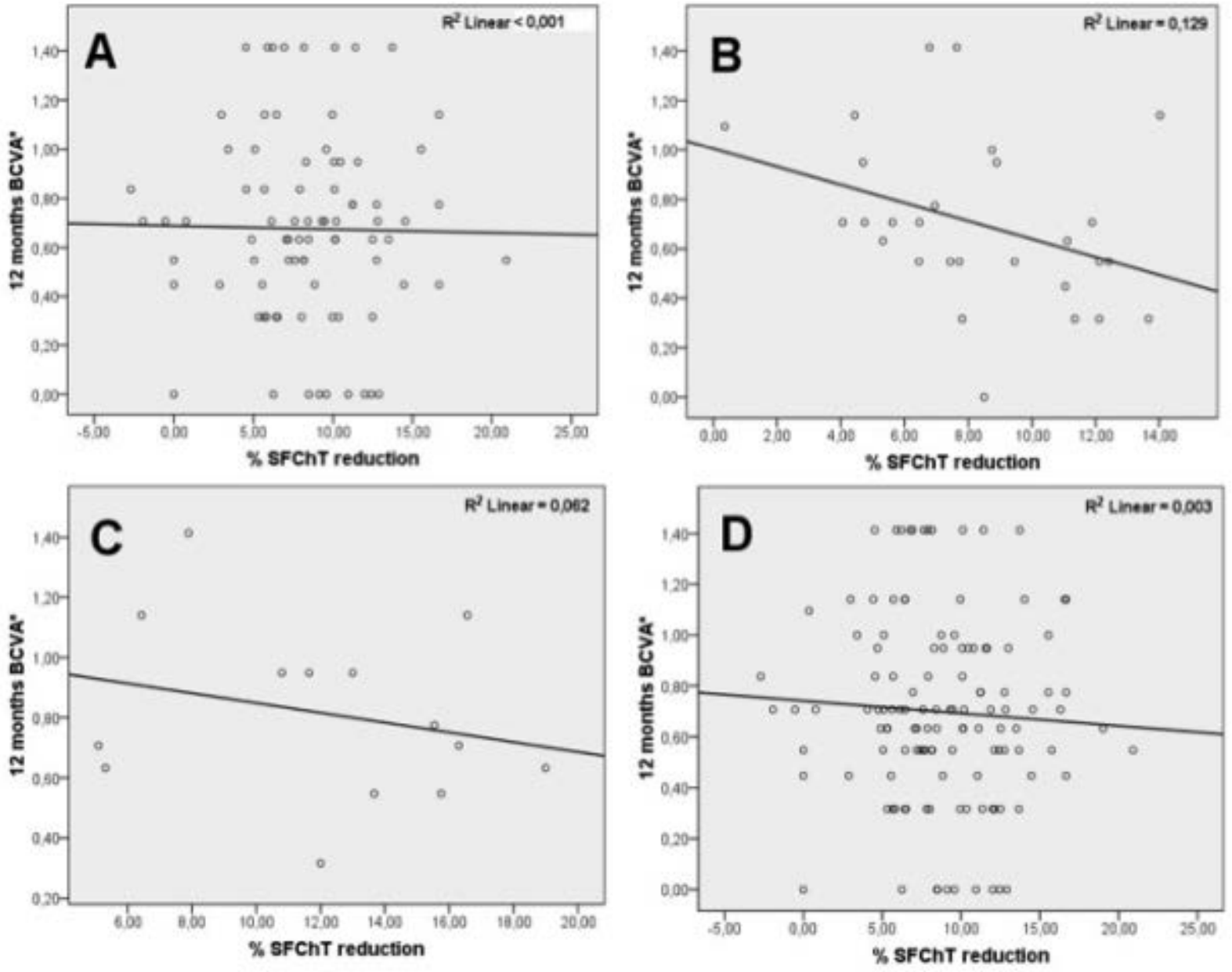

A
R² Linear < 0,001
12 months BCVA*
% SFChT reduction
B
R² Linear = 0,129
12 months BCVA*
% SFChT reduction
C
R² Linear = 0,062
12 months BCVA*
% SFChT reduction
D
R² Linear = 0,003
12 months BCVA*
% SFChT reduction

Figure legends

Figure 1: Subfoveal choroidal thickness at baseline, 3, 6 and 12 months according to neovascular age-related macular degeneration subtypes.

SFChT: subfoveal choroidal thickness

PCV: polypoidal choroidal vasculopathy

RAP: retinal angiomatous proliferation

Figure 2: Correlation between the change in the best-corrected visual acuity over the 12-month follow-up period, and the percentage of subfoveal choroidal thickness reduction in the neovascular age-related macular degeneration subtypes (A:typical; B: polypoidal choroidal vasculopathy; C: retinal angiomatous proliferation) and in all the study patients treated with anti-VEGF agents(D).

% SFChT reduction= (1–baseline SFChT/SFChT at 12 mo) ×100

BCVA*: square root of best-corrected visual acuity

July 24, 2017

S. Wolf
Editor-in-Chief
Ophthalmologica

Dear Dr. Wolf:

I wish to submit an original research article for publication in Retina, titled "**Subfoveal choroidal thickness in eyes with neovascular age-related macular degeneration treated with anti-vascular endothelial growth factor agents**". The paper was coauthored by Carlos Eduardo dos Reis Veloso and Márcio Bittar Nehemy.

In this study, we aimed to assess the subfoveal choroidal thickness (SFChT) and the effect of treatment with anti-vascular endothelial growth factor (VEGF) agents on the SFChT in age-related macular degeneration (AMD) subtypes. We believe that our study makes a significant contribution to the literature because we clearly showed there is no correlation between baseline SFChT and final visual acuity at 12 months. Moreover, this study also showed that there is a decrease in the SFChT in all AMD subtypes treated with anti-VEGF over a 12-month follow-up period. A higher percentage of reduction in SFChT was observed in patients diagnosed with retinal angiomatous proliferation.

Furthermore, we believe that this paper will be of interest to the readership of your journal because, to our knowledge, no previous studies have evaluated the relationship between SFChT and visual outcome in AMD subtypes.

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare. All authors of this paper concur with the submission.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,
Tereza Cristina Moreira Kanadani
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Maranhão 1007 street, apt.2201, Belo Horizonte-Brazil, zip code:30150-331
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CONCLUSÃO DO TERCEIRO TRABALHO:

Este trabalho permitiu concluir que não existe correlação entre a ESC basal e a acuidade visual final aos doze meses. Além disso, este estudo também mostrou que há diminuição da ESC em todos os subtipos de DMRI tratados com agentes anti-VEGF ao longo do período de doze meses de seguimento. Observou-se maior percentual de redução na ESC em pacientes com diagnóstico de RAP. Não está claro se essa diminuição representa a história natural dos diferentes subtipos de DMRI, ou se está relacionada ao tratamento com agentes anti-VEGF. Não houve correlação entre a ESC basal e a AV final, nem entre o número de injeções utilizadas no tratamento.

DISCUSSÃO:

A DMRI é doença degenerativa que afeta a mácula, sendo uma das principais causas de cegueira em todo o mundo.[1-4] A DMRI avançada é caracterizada por neovascularização sub-retiniana, ou atrofia geográfica. Embora a DMRI neovascular esteja presente em até 20% de todos os casos, essa forma é responsável pela maior porcentagem de pacientes com perda visual significativa devido a seu curso progressivo e agressivo. Sem tratamento, a maioria dos pacientes com a forma neovascular terá uma perda visual significativa dentro de um ano.[49]

O tratamento da DMRI apresentou avanços extraordinários nos últimos anos. Esses avanços se devem fundamentalmente a novos conhecimentos sobre a sua fisiopatologia, que propiciaram tratamentos mais precoces e direcionados aos mecanismos da doença e ao significativo avanço nos meios propedêuticos – com destaque para a OCT- SD – que permitiram refinada visualização da microestrutura macular.

O uso dos medicamentos anti-VEGF para o tratamento da DMRI exsudativa possibilita hoje a melhora ou estabilização da acuidade visual em cerca de 90% dos casos tratados. [50,51] Uma vez atingida essa importante meta, impunham-se estudos adicionais que deveriam analisar os fatores que pudessem influenciar os resultados desse tratamento. Igualmente importante seria analisar os eventuais efeitos dos referidos medicamentos na microestrutura macular. Foi em tal contexto que esta tese foi planejada e elaborada.

A DMRI é uma doença com fisiopatologia complexa e multifatorial. Seria obviamente impossível abordar todos os fatores que pudessem influenciar seu tratamento, bem como todos os eventuais efeitos dos mencionados tratamentos na microestrutura macular. Ao pesquisarmos na literatura tópicos de potencial interesse, mas ainda não completamente estudados, decidiu-se, neste estudo, avaliar a influência da adesão vitreomacular na resposta

terapêutica aos anti-VEGF e os eventuais efeitos destes medicamentos na espessura da coroide.

A discussão dos resultados desta pesquisa já foi realizada nos respectivos textos, publicados nas revistas especializadas, e que fazem parte do corpo desta tese. Sendo assim, e para evitar desnecessárias redundâncias, apresenta-se a seguir apenas as principais conclusões deste trabalho.

CONCLUSÕES FINAIS:

Considerando-se a amostra de pacientes com DMRI neovascular, com tratamento com agentes anti-VEGF, com 3 doses de carregamento, seguidos pelo regime *pro re nata*, este estudo permitiu as seguintes conclusões:

Conclusões primárias:

- Em olhos com DMRI neovascular, o tratamento com agentes anti-VEGF levou a redução estatisticamente significativa da espessura macular central após um, dois, três, seis e doze meses.

- Em olhos com DMRI neovascular, a diminuição da espessura macular central após tratamento com agentes anti-VEGF foi semelhante em olhos com e sem adesão vitreomacular, após um, dois, três, seis e doze meses.

- Olhos com DMRI neovascular e adesão vitreomacular apresentaram menor resposta funcional, a curto prazo (três meses), que olhos com DMRI neovascular sem adesão vitreomacular. Entre três e doze meses, não houve diferença nos resultados funcionais entre os olhos com e sem adesão vitreomacular.

- Não houve diferença estatisticamente significativa no número de injeções de agentes anti-VEGF nos olhos com e sem adesão vitreomacular.

- Injeções intravítreas de agentes anti-VEGF comumente utilizadas, raramente induziram descolamento posterior do vítreo em pacientes com DMRI neovascular.

- Olhos com DMRI neovascular e adesão vitreomacular focal tiveram maior chance de desenvolver descolamento do vítreo posterior que olhos com ampla área de adesão vitreomacular.

- Houve diminuição da espessura subfoveal da coroide em todos os subtipos de DMRI tratados com agentes anti-VEGF ao longo do período de doze meses de seguimento.

- Observou-se maior percentual de redução na espessura subfoveal da coroide em olhos com proliferação angiomatosa da retina (RAP) que nos olhos com vasculopatia polipoidal (PCV) ou DMRI típica. Não houve diferença estatisticamente significativa no percentual de redução da espessura da coroide entre os olhos com PCV e DMRI típica.

- Não houve correlação entre a espessura subfoveal da coroide no *baseline* e a acuidade visual final após doze meses de tratamento.

- Não houve correlação entre a espessura subfoveal da coroide no *baseline* e o número de injeções em doze meses de tratamento.

Conclusões secundárias:

- No *baseline*, pacientes com DMRI neovascular, do sexo masculino, tiveram maior prevalência de adesão vitreomacular que pacientes do sexo feminino.

- No *baseline,* os pacientes com DMRI neovascular e idade mais avançada apresentaram maior prevalência de descolamento de vítreo posterior que os pacientes menos idosos com DMRI neovascular.

- Não foi observada diferença estatisticamente significativa entre os grupos com e sem adesão vitreomacular em relação ao estado do cristalino.

- Não houve correlação estatisticamente significativa entre adesão vitreomacular e os subtipos de DMRI neovascular estudados: RAP, PCV e DMRI típica.

- Não foi observada diferença estatisticamente significativa na AV no *baseline* entre os três subtipos de DMRI neovascular: RAP, PCV e DMRI típica.

- O fator mais importante correlacionado com a AV aos doze meses após o tratamento foi a acuidade visual no *baseline.*

- Os pacientes com diagnóstico de PCV apresentaram, em média, maior espessura subfoveal da coroide no *baseline*, enquanto os pacientes com RAP tiveram, em média, menor espessura subfoveal da coroide.

- Não houve correlação significativa entre a espessura subfoveal da coroide e a idade dos pacientes, no *baseline*.

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APÊNDICE

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

ANÁLISE DA MICROESTRUTURA MACULAR PELA TOMOGRAFIA DE COERÊNCIA ÓPTICA DE PACIENTES PORTADORES DE DEGENERAÇÃO MACULAR RELACIONADA À IDADE TRATADOS COM ANTIANGIOGÊNICOS

Introdução: Você está sendo convidado a participar do projeto de pesquisa citado acima. Antes de tomar qualquer decisão, é importante que você leia e compreenda as seguintes explicações sobre o procedimento proposto. Esta declaração descreve o objetivo, procedimento, benefícios e riscos do estudo, e o seu direito de sair do estudo a qualquer momento. Nenhuma garantia ou promessa pode ser feita sobre o resultado do estudo. Estas informações estão sendo dadas para esclarecer quaisquer dúvidas sobre a pesquisa proposta, antes de obter o seu consentimento.

Objetivo: O objetivo do estudo é analisar a importância da Interface vitreomacular e a espessura da coroide na resposta ao tratamento antiangiogênico em pacientes portadores da forma exsudativa da Degeneração macular relacionada à idade (DMRI).

Resumo: A DMRI é uma doença progressiva afetando a retina central com envolvimento primário das camadas externas da retina, sendo responsável pela principal causa de perda visual grave em países desenvolvidos.[1] A patogênese e os fatores de risco para o desenvolvimento da DMRI não são completamente entendidos.[2] Estudos prévios descreveram a relação entre o vítreo posterior e a DMRI. A adesão vitreomacular persistente (AVM) é considerada um fator de risco para o desenvolvimento de DMRI exsudativa , enquanto que o descolamento do vítreo posterior (DVP) pode proteger contra esta forma da doença.[3-6] A AVM anormal pode ter um papel fundamental na resposta ao tratamento da DMRI exsudativa. A terapia intravítrea com agentes que inibem o crescimento endotelial vascular (anti-VEGF) , como o ranibizumabe, o bevacizumabe e o aflibercept são considerados tratamento ouro para a DMRI exsudativa.[7] Alguns pacientes se mostram não-responsivos ,

mostrando resistência ao tratamento com agentes anti-VEGF.[8] Estudos genéticos e da interface vitreomacular têm sido conduzidos para determinar quais olhos respondem melhor ao tratamento.[9-11] Um estudo retrospectivo recente usando a tecnologia time-domain para tomografia de coerência óptica (OCT) mostrou que a AVM está associada a um pior prognóstico visual após tratamento intravítreo com agentes anti-VEGF para DMRI exsudativa, sugerindo que forças tracionais crônicas possam antagonizar o efeito dessas drogas.[11] Diversos estudos clínicos têm enfatizado a incidência de AVM em pacientes com DMRI usando a OCT para configurar a interface vitreomacular. Uma alta proporção de AVM tem sido observada em pacientes com DMRI comparada com o grupo controle, sugerindo descolamento anormal do vítreo na população com DMRI. [12] A configuração da interface vitreomacular parece ter um importante efeito no prognóstico visual e necessidade de retratamento em pacientes com DMRI exsudativa. Em pacientes com DVP total, uma baixa frequência de tratamento antiangiogênico pode ser possível, enquanto que em pacientes com AVM há uma maior necessidade de retratamento. [13]

Os pacientes do estudo foram submetidos a exame oftalmológico completo, além de exame de retinografia colorida e fluorescente e tomografia de coerência óptica conforme rotina da clínica para portadores de DMRI. Pacientes com a forma exsudativa da doença foram submetidos ao tratamento antiangiogênico, também conforme rotina praticada na clínica. Portanto não haverá risco ou ônus adicionais ao participante do estudo.

Critérios de inclusão e exclusão: Serão incluídos no estudo os pacientes examinados no serviço de retina e vítreo do Instituto da Visão (Minas Gerais – Brasil), recém diagnosticados com degeneração macular relacionada à idade forma exsudativa, que apresentarem a idade acima de 50 anos. Pacientes com DMRI e outras doenças maculares como alta miopia, estrias angióides, coriorretinopatia serosa central e retinopatia diabética serão excluídos.

Risco ao participante: Não haverá risco adicional ao participante, os exames propostos pelo estudo são rotineiramente realizados e necessários para o tratamento de pacientes com DMRI. A angiografia envolve injeção de contraste endovenoso com os riscos de hipersensibilidade inerente ao procedimento. Complicações da angiografia incluem náuseas e vômitos,

prurido (coceira), abscesso no local de injeção do contraste, afecções raras como edema de glote e choque anafilático. O Instituto da Visão possui a infraestrutura, aparelhos e equipamentos necessários para a realização dos exames e tratamento das possíveis complicações.

Confidencialidade: Os registros de sua participação neste estudo serão mantidos confidencialmente até onde é permitido por lei e todas as informações estarão restritas à equipe responsável pelo projeto. No entanto, o pesquisador e sob certas circunstâncias, o Comitê de Ética em Pesquisa/UFMG, poderão verificar e ter acesso aos dados confidenciais que o identificam pelo nome. Qualquer publicação dos dados não o identificará. Ao assinar este formulário de consentimento, você autoriza o pesquisador a fornecer seus registros médicos para o Comitê de Ética em Pesquisa/UFMG.

Desligamento: A sua participação neste estudo é voluntária e sua recusa em participar ou seu desligamento do estudo não envolverá penalidades ou perda de benefícios aos quais você tem direito. Você poderá cessar sua participação a qualquer momento sem afetar seu acompanhamento médico em andamento.

Compensação: Você não receberá qualquer compensação financeira por sua participação no estudo.

Emergência / contato com a Comissão de Ética: Durante o estudo, se você tiver qualquer dúvida ou apresentar qualquer problema médico, contate a Dra. Tereza Cristina Moreira Kanadani no telefone (31) 99974-2112 ou a Comissão de Ética no telefone 3248-9364 (UFMG)

Consentimento: Li e entendi as informações precedentes. Tive a oportunidade de fazer perguntas e todas as minhas dúvidas foram respondidas a contento. Este formulário está sendo assinado voluntariamente por mim, indicando o meu consentimento para participar do estudo, até que eu decida o contrário.

Eu,....., abaixo assinado(a), concordo de livre e espontânea vontade em participar como voluntário(a) do estudo “**ANÁLISE DA MICROESTRUTURA MACULAR PELA TOMOGRAFIA DE COERÊNCIA ÓPTICA DE PACIENTES PORTADORES DE DEGENERAÇÃO MACULAR RELACIONADA À IDADE TRATADOS COM ANTIANGIOGÊNICOS”**

ANEXOS

PARECER DO COMITÊ DE ÉTICA EM PESQUISA (COEP) DA UNIVERSIDADE FEDERAL DE MINAS GERAIS

UNIVERSIDADE FEDERAL DE MINAS GERAIS

PARECER DO COLEGIADO

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ANÁLISE DA MICROESTRUTURA MACULAR ATRAVÉS DA TOMOGRAFIA DE COERÊNCIA ÓPTICA DE DOMÍNIO SPECTRAL EM PACIENTES PORTADORES DE DEGENERAÇÃO MACULAR RELACIONADA À IDADE FORMA EXSUDATIVA

Pesquisador: Márcio Bittar Nehemy

Área Temática:

Versão: 1

CAAE: 82155315.8.0000.5149

Instituição Proponente: UNIVERSIDADE FEDERAL DE MINAS GERAIS

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.469.461

Apresentação do Projeto:

A degeneração macular relacionada à idade (DMRI) é uma desordem progressiva afetando a retina central com envolvimento primário das camadas externas da retina, sendo responsável pela principal causa de perda visual severa em países desenvolvidos. A patogênese e os fatores de risco para o desenvolvimento da DMRI não são completamente entendidos.2 Estudos prévios descreveram a relação entre o vítreo posterior e a DMRI. A adesão vitreomacular persistente (AVM) é considerada um fator de risco para o desenvolvimento de DMRI exsudativa , enquanto que o descolamento do vítreo posterior (DVP) pode proteger contra esta forma da doença.3-6 A AVM anormal pode ter um papel fundamental na resposta ao tratamento da DMRI exsudativa. A terapia intravítrea com agentes que inibem o crescimento endotelial vascular (anti-VEGF) , como o ranibizumabe e o bevacizumabe , são considerados tratamento ouro para a DMRI exsudativa. Alguns pacientes se mostram não-responsivos , mostrando resistência ao tratamento com agentes anti-VEGF.8 Estudos genéticos e da interface vitreomacular têm sido conduzidos para determinar quais olhos respondem melhor ao tratamento.9-11 Um estudo retrospectivo recente usando a tecnologia time-domain para tomografia de coerência óptica (OCT) mostrou que a AVM está associada a um pior prognóstico visual após tratamento intravítreo com agentes anti-VEGF para DMRI exsudativa, sugerindo que forças tracionais crônicas possam antagonizar o efeito dessas

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drogas.11 Diversos estudos clínicos têm enfatizado a incidência de AVM em pacientes com DMRI usando a OCT para configurar a interface vitreomacular. Uma alta proporção de AVM tem sido observada em pacientes com DMRI comparada com o grupo controle, sugerindo descolamento anormal do vítreo na população com DMRI. A configuração da interface vitreomacular parece ter um importante efeito no prognóstico visual e necessidade de retratamento em pacientes com DMRI exsudativa. Em pacientes com DVP total, uma baixa frequência de tratamento anti-angiogênico pode ser possível, enquanto que em pacientes com AVM há uma maior necessidade de retratamento. 13 O objetivo do estudo será analisar de forma prospectiva a importância da interface vitreomacular no curso do tratamento anti-angiogênico em pacientes portadores de DMRI forma exsudativa.

Os pacientes do estudo serão submetidos a exame oftalmológico completo, além de exame de retinografia colorida e fluoresceína e tomografia de coerência óptica conforme rotina da clínica para portadores de DMRI. Pacientes com a forma exsudativa da doença serão submetidos ao tratamento anti-angiogênico, também conforme rotina praticada na clínica.

Objetivo da Pesquisa:

Segundo o pesquisador, objetivo Primário é:

1)Avaliar o prognóstico das alterações na IVM em pacientes portadores de DMRI forma exsudativa.

2)Correlacionar as alterações na IVM com a acuidade visual e medidas de CRT pré e pós-tratamento anti-angiogênico.

3)Correlacionar as alterações na SFChT com a acuidade visual pré e pós-tratamento anti-angiogênico

Avaliação dos Riscos e Benefícios:

Segundo o pesquisador, não haverá risco adicional ao participante, os exames propostos pelo estudo são rotineiramente realizados e necessários para o tratamento de pacientes com DMRI. A angiografia envolve injeção de contraste endovenoso com os riscos de hipersensibilidade inerente ao procedimento. Complicações da angiografia incluem náuseas e vômitos, prurido (coceira), abscesso no local de injeção do contraste, afecções raras como edema de glote e choque anafilático. O Instituto da Visão possui a infraestrutura, aparelhos e equipamentos necessários para a realização dos exames e tratamento das possíveis complicações.

Benefícios: Avaliação de um possível melhoria em pacientes com DMRI

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Comentários e Considerações sobre a Pesquisa:

A pesquisa é relevante no campo da oftalmologia.

Considerações sobre os Termos de apresentação obrigatória:

Foi apresentado os seguintes documentos:

-TCLE

- Parecer consubstanciado aprovado pelo Departamento de Oftalmologia

- Folha de rosto assinada pelo pesquisador e diretor da Faculdade de Medicina

Recomendações:

Não se aplica

Conclusões ou Pendências e Lista de Inadequações:

SMJ, sou favorável à aprovação do projeto de pesquisa

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_544796.pdf	17/01/2018 16:25:45		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.docx	17/01/2018 16:25:23	TEREZA CRISTINA MOREIRA KANADANI	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEPFDF.pdf	17/01/2018 16:25:10	TEREZA CRISTINA MOREIRA KANADANI	Aceito
Outros	Parecer_Tereza_Kanadani.pdf	17/01/2018 16:24:48	TEREZA CRISTINA MOREIRA KANADANI	Aceito
Folha de Rosto	Folha de Rosto.pdf	15/07/2015 15:48:11		Aceito
Projeto Detalhado / Brochura Investigador	projeto final.pdf	25/06/2015 15:59:09		Aceito
Projeto Detalhado / Brochura Investigador	projeto final.docx	25/06/2015 15:59:02		Aceito

Situação do
Aprovado

Necessita Apreciação da CONEP:

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Continuação do Parecer: 2468401

Não

BELO HORIZONTE, 19 de Janeiro de 2018

Assinado por:
Vivian Resende
(Coordenador)

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COMITÊ DE ÉTICA EM PESQUISA - COEP

Projeto: CAAE 82155315.8.0000.5149

Interessado(a): Prof. Márcio Bittar Nehemy
Depto. Oftalmologia e Otorrinolaringologia
Faculdade de Medicina - UFMG

DECISÃO

O Comitê de Ética em Pesquisa da UFMG – COEP aprovou, no dia 19 de janeiro de 2018, o projeto de pesquisa intitulado "**Análise da microestrutura macular através da tomografia de coerência óptica de domínio spectral em pacientes portadores de degeneração macular relacionada à idade forma exsudativa**" bem como o Termo de Consentimento Livre e Esclarecido.

O relatório final ou parcial deverá ser encaminhado ao COEP um ano após o início do projeto através da Plataforma Brasil.

Profa. Dra. Vivian Resende
Coordenadora do COEP-UFMG