Age-related macular degeneration with choroidal neovascularization in the setting of pre-existing geographic atrophy and ranibizumab treatment. Analysis of a case series and revision paper*

Avaliação da resposta da injeção intravítrea de ranibizumab em pacientes com neovascularização de coróide da degeneração macular relacionada à idade com atrofia geográfica extensa pré-existente e revisão da literatura

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ABSTRACT

Purpose: *To report the response of choroidal neovascularization (CNV) to intravitreal ranibizumab treatment in the setting of age-related macular degeneration (AMD) with extensive pre-existing geographic atrophy (GA) and a revision paper.* ***Methods:*** *This is a revision paper and a retrospective case series of 10 eyes in nine consecutive patients from a photographic database. The patients were actively treated with ranibizumab for neovascular AMD with extensive pre-existing GA. Patients were included if they had GA at or adjacent to the foveal center that was present before the development of CNV. The best corrected visual acuity and optical coherence tomography (OCT) analysis of the central macular thickness were recorded for each visit. Serial injections of ranibizumab were administered until there was resolution of any subretinal fluid clinically or on OCT. Data over the entire follow-up period were analyzed for overall visual and OCT changes. All patients had been followed for at least 2 years since diagnosis.* ***Results:*** *The patients received an average of 6 ± 3 intravitreal injections over the treatment period. Eight eyes had reduced retinal thickening on OCT. On average, the central macular thickness was reduced by 94 ± 101 µm. Eight eyes had improvement of one or more lines of vision, whereas one eye had dramatic vision loss and one had no change. The average treatment outcome for all patients was -0.07 ± 4.25 logMAR units, which corresponded to a gain of 0.6 ± 4.4 lines of Snellen acuity. The treatment resulted in a good anatomic response with the disappearance of the subretinal fluid, improved visual acuity, and stabilized final visual results.* ***Conclusion:*** *The results of this case series suggest that the use of an intravitreal anti-vascular endothelial growth factor (VEGF) agent (ranibizumab) for CNV in AMD with extensive pre-existing GA is effective. Our results are not as striking as published results from large-scale trials of anti-VEGF therapy for subfoveal CNV, presumably due to the limitation in the baseline visual acuity caused by the underlying GA. The good anatomic response with the disappearance of the subretinal fluid, improved visual acuity, and stabilized final visual results were consistent with other ranibizumab studies.*

Keywords: *Macular degeneration; Geographic atrophy; Choroidal neovascularization; Antibodies, monoclonal/therapeutic use; Retina*

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Resumo

Investigar os resultados da injeção intravítrea de Ranibizumab em pacientes com neovascularização de coróide da degeneração macular relacionada a idade, com atrofia geográfica extensa, pré-existente e revisão da literatura. **Métodos:** Este é um artigo de revisão e também um estudo retrospectivo de 9 pacientes, 10 olhos com neovascularização de coróide da degeneração macular relacionada à idade, com atrofia geográfica extensa, pré-existente. Os pacientes incluídos apresentaram atrofia geográfica, envolvendo a fóvea ou adjacente, antes do desenvolvimento da neovascularização de coróide. A melhor correção visual e o exame de tomografia de coerência óptica (OCT) com analise da espessura macular foram registrados em cada visita. As injeções de ranibizumab intravítrea foram feitas até a resolução do líquido sub-retiniano pelo OCT e clinicamente. Todos os pacientes tinham seguimento de 6 meses do diagnostico a 2 anos, com média de 16 meses. **Resultados:** 10 olhos de 9 pacientes incluídos receberam uma média de 6 ± 3 injeções intravítreas de ranibizumab, sendo que 8 apresentaram redução do espessamento macular pelo OCT. A mácula teve o espessamento reduzido entre 94 ± 101 microns, 8 olhos tiveram melhora de 1 ou mais linhas de visão, um olho teve acentuada diminuição da visão.e um outro não teve alteração. A media do resultado do tratamento em logMAR era -0,07 ± 4.25 correlacionando um ganho de visão na tabela de Snellen entre 0,6 ± 4.4linhas de visão. **Conclusão:** Estes resultados sugerem que o uso do Ranibizumab intravítreo para neovascularização de coróide da degeneração macular relacionada à idade em extensa atrofia geográfica pré-existente é efetivo. Existem, entretanto, dificuldades na avaliação da acuidade visual destes pacientes em virtude da extensa Atrofia Geográfica que apresentavam e sobre esta ainda as complicações da neovascularização de coróide, se comparados a casos em que a neovascularização de coróide não ocorre em atrofia geográfica pré-existente.

Descritores: Degeneração macular; Atrofia geográfica; Neovascularização de coróide; Anticorpos monoclonais/uso terapêutico; Retina

Introduction

Geographic atrophy (GA) is defined in the AREDS study as one or more well-defined, usually more or less circular, patches of partial or complete depigmentation of the retinal pigment epithelium (RPE), typically with exposure of underlying large choroidal blood vessels[1]. GA associated with age-related macular degeneration (AMD) is estimated to affect nearly 1% of the US population, with this prevalence expected to increase by 50% by the year 2020[2]. GA is a form of advanced age-related macular degeneration (AMD) that causes central visual loss and evolves gradually in the central fovea[1].

Histopathological sections of GA show thinning or absence of the RPE, closure of the choriocapillaris, and degeneration of the overlying photoreceptors[3,4]. It has been reported[3,4] that the site of the initial appearance of GA was previously occupied by drusen, which was large (125 ì m in diameter) in 96% of cases. In 83% of eyes, the largest drusen was 250 ì m in diameter. The drusen was usually confluent, with at least two in contact, but it is sometimes extensive enough to form plaques of drusenoid material. In addition, the GA is nearly always preceded by the appearance of hyperpigmentation overlying drusen, followed by regression of the drusen and the appearance of hypopigmentation, sometimes accompanied by refractile deposits. Furthermore, in some eyes, different precursor lesions might appear simultaneously. Research[5,6] has shown that the strongest predictor of the subsequent spread of GA is growth in the previous 2 years. Increased fundus autofluorescence outside atrophic patches of GA may also be an important predictor of subsequent progression[7].

Another finding in advanced AMD is choroidal neovascularization (CNV)[8]. Although hyperpigmentation and hypopigmentation abnormalities of the RPE and drusen are precursors of GA and CNV, these are related only because they are advanced forms of age-related macular degeneration[8,9].

The coexistence of GA and CNV has been proved histopathologically[3,4,10]. Some studies[11,12] have shown that the vascular endothelial growth factor (VEGF)-specific monoclonal antibodies, ranibizumab and bevacizumab, improve the visual acuity in patients with AMD and subfoveal CNV[11,14]. In the Marina[11] and Anchor[12] trials with ranibizumab, 94.6% and 96.4% of the patients avoided a 15-letter VA decrease, respectively. Moreover, 34% and 43% of patients gained at least 15 letters of VA, respectively. The final mean improved by 7.2 and 11.3 letters in the Marina[11] and Anchor[12] trials, respectively. However, other treatments have been used, including laser photocoagulation[15,16], verteporfin photodynamic therapy (PDT)[17], photothrombosis with indocyanine green[18], and pegaptanib sodium intravitreal injection[19].

This report is a revision paper and investigated the results of ranibizumab intravitreal monotherapy in the treatment of CNV in the context of AMD with extensive pre-existing GA.

Methods

This is a revision paper and a retrospective cases series study from a photographic database center of 10 eyes in 9 consecutive patients under active treatment with ranibizumab monotherapy for neovascular AMD in the setting of pre-existent Geographic Atrophy. Patients were included if they had GA at or adjacent to the central fovea that was present before the development of CNV (Figures 1 to 7). The exclusion criterion was no prior treatment of CNV from AMD with extensive pre-existing GA only permissible in the AREDS formulation[20]. The best corrected visual logMAR and Snellen schedule, color fundus photography, fluorescein angiography, and optical coherence tomography (OCT) were obtained each visit. We used Heidelberg OCT to analyze the central macular thickness, which we recorded each month. Ranibizumab monotherapy was injected intravitreal monthly until there was resolution of the subretinal fluid clinically or by OCT (criteria of retreatment) for a 2-year period. Data on the overall visual and OCT changes over the entire follow-up 2-year period were analyzed. All patients were followed for at least 6 months (mean 16 months) and up to 2 years after diagnosis.

Results

The study included 10 eyes from 9 patients who had been treated with ranibizumab as monotherapy. The patients received an average of 6 ± 3 intravitreal injections over the treatment period. Eight eyes had reduced retinal thickening on OCT. On average, the central macular thickness was reduced by 94 ± 101 µm. Eight eyes had an improvement of one or more lines of vision, whereas one eye had dramatic vision loss and one eye hasn't change in his vision . The average treatment outcome for all patients was –0.07 ± 4.25 logMAR units, which corresponded to a gain of 0.6 ± 4.4 lines of Snellen acuity.

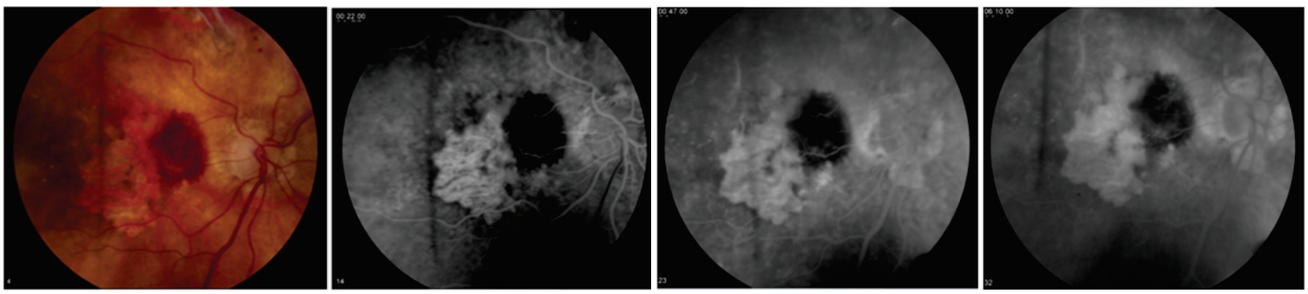

Figure 1: Choroidal hemorrhage from occult CNV in geographic atrophy, patient number 6

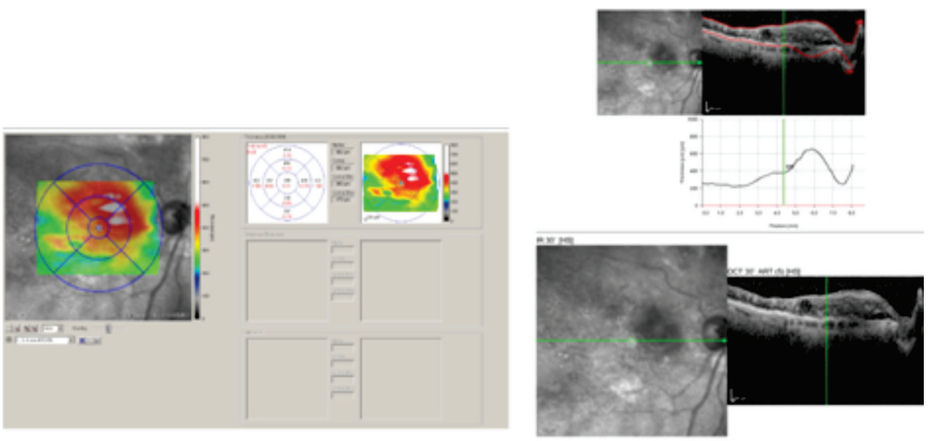

Figure 2: Patient number 6: OCT before treatment showing thinning along the temporal aspect of the central macula, and some diffuse thickening as well as some cystoid abnormalities around the nasal aspect of the central macula

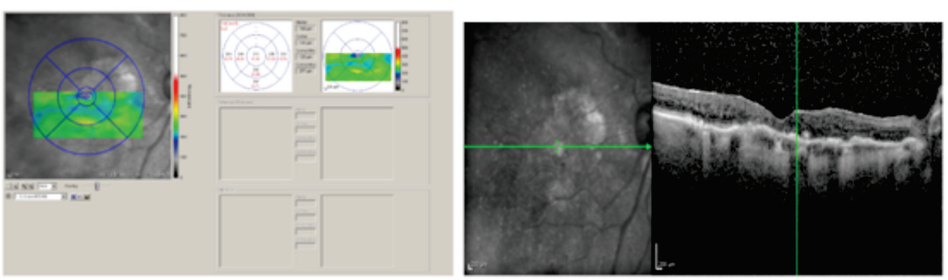

Figure 3: OCT after treatment showing resolution of findings

Choroidal neovascularization and GA are advanced forms of AMD according the AREDS reports[1] and others[8,10]. When CNV develops in eyes with GA, it can cause both an abrupt drop in visual acuity and progression to central vision loss.[8,10] The AREDS data[2] indicate that about one-third of the participants had central GA at the time when GA was first identified, there was a median time to progression from GA to central GA of 2 years. Visual acuity is often decreased before the development of central GA; for those who do not develop CNV, vision is expected to decline an additional 22 letters on average during the next 5 years. Eyes that develop subsequent CNV have an even worse prognosis.

The reported 2-year rate of 18% and 4-year rate of 34% of CNV in eyes with GA is compatible with the MPS study[15] and that of Sunness et al.[10] Other studies[21,23] reported similar rates of CNV developing in eyes with GA . This is a high incidence and disproves the impression that GA protects against the development of CNV. In a study of the treatment of extrafoveal CNV from AMD, the MPS[15] included 11 participants with GA and without CNV in the fellow eye at baseline. Over a 5-year period, five (45%) patients went on to develop CNV in the GA eye. The MPS report included participants from the juxtafoveal and subfoveal AMD trials.

In a case report on a patient with GA[3], with clinicopathological evaluation, in whom the existence of CNV was not initially suspected and a fluorescein angiogram had not revealed CNV, the researchers noted that CNV developed in one eye with GA in areas of residual choriocapillaris and pigment epithelium, while no CNV developed in the fellow eye with GA despite breaks in Bruch's membrane, presumably because the breaks occurred in areas without residual choriocapillaris and RPE, similar to the study by Sunness et al.[10] Similar to our study, CNV did not grow over atrophy and was seen to develop at the edge of the GA (Yannuzzi L, personal communication) or in spared areas within the GA.

In our study, eight eyes had improvement of one or more lines of vision, whereas one eye had dramatic vision loss and one

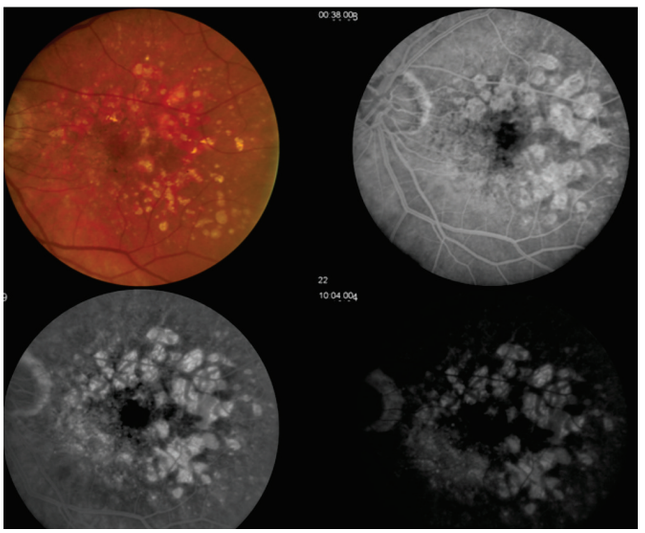

Figure 4: Extensive geographic atrophy, patient number 7

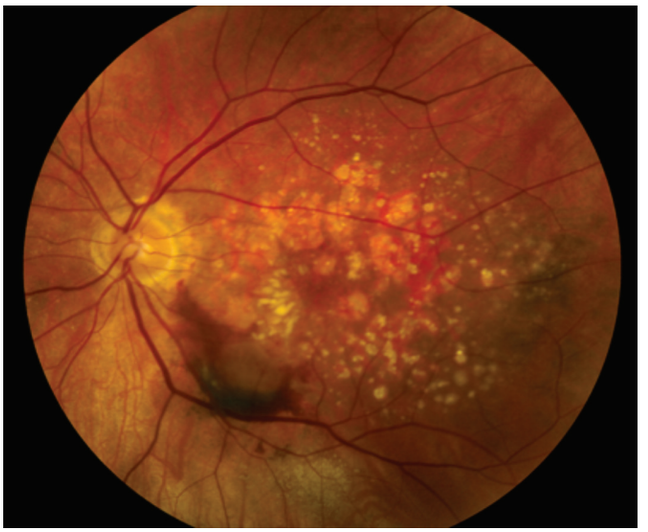

Figure 5: Choroidal hemorrhage from occult CNV in geographic atrophy, patient number 7

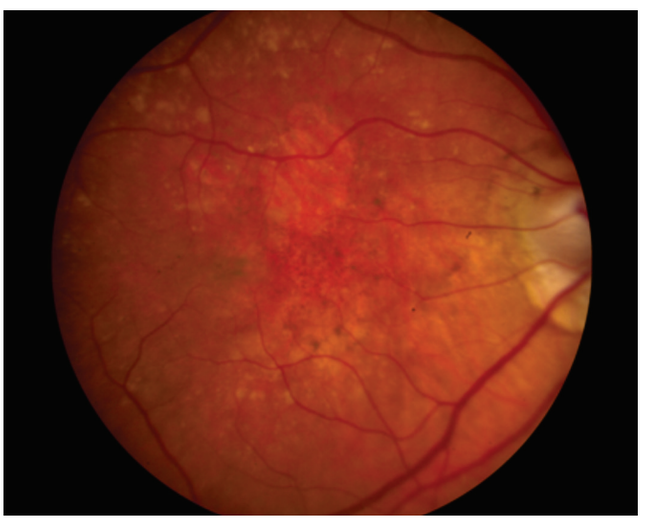

Figure 6: Extensive geographic atrophy, patient number 9

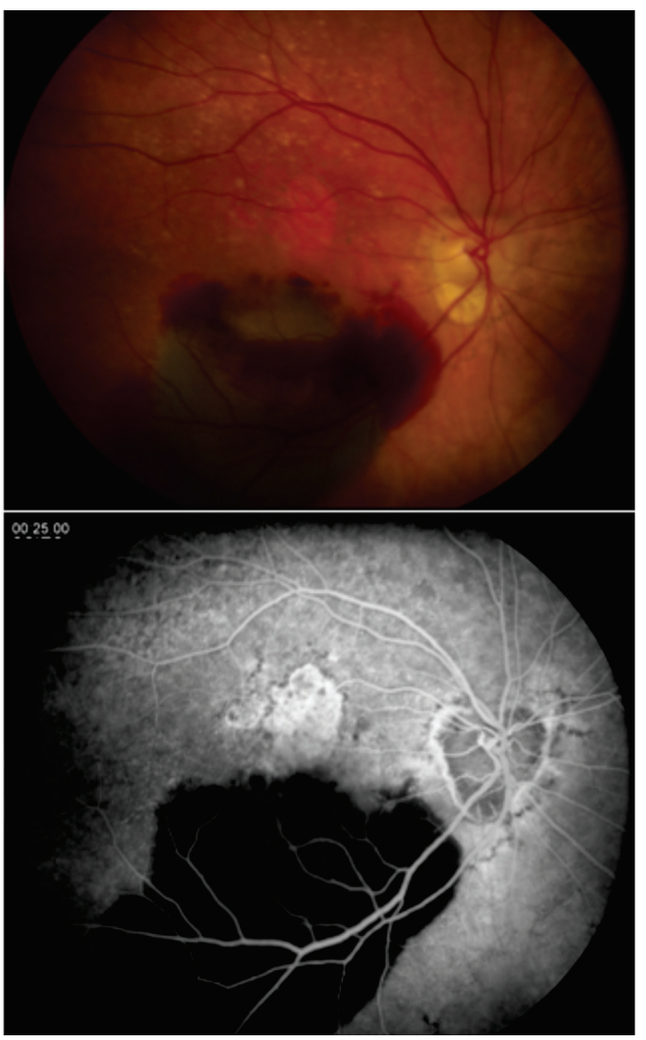

Figure 7: Choroidal hemorrhage from occult CNV in geographic atrophy, patient number 9

had no change.

The patients received an average of 6 ± 3 intravitreal injections over the treatment period. Most of them (8 out 9 patients) had reduced retinal thickening on OCT. On average, the central macular thickness was reduced by 93 ± 105 µm. The average treatment outcome for all patients was –0.07 ± 4.25 logMAR units, which corresponded to a gain of 0.6 ± 4.4 lines of Snellen acuity.

The Marina[11] and Anchor[12] studies proved the efficacy of anti-VEGF therapy with ranibizumab in the treatment of subfoveal CNV. Eight of our 10 patients improved their vision with ranibizumab treatment for CNV in AMD with extensive pre-existing GA and reports of ranibizumab treatment of choroidal neovascularization in the setting of pre-existing Geographic Atrophy from AMD[24,25] with similar results as: good anatomic response with disappearance of the subretinal fluid, improved visual acuity and stabilized final visual results consistent with others ranibizumab studies[11,12,24,25].

Conclusion

The results of this cases series suggest that the use of an intravitreal anti-VEGF agent (ranibizumab) for CNV in AMD with extensive pre-existing GA is effective for these patients. Our results are not as striking as the results of large-scale trials of anti-VEGF therapy for subfoveal CNV, presumably due to the limitation of the baseline visual acuity caused by the underlying GA.

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