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Guidelines in focus

Age-related macular degeneration

Degeneração macular relacionada à idade

Conselho Brasileiro de Oftalmologia (Brazilian Council of Ophthalmology)

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Description of the evidence collection method
A literature review of the scientific articles in this guideline was performed in MEDLINE, Cochrane, and SciELO databases. The search for evidence came from real clinical scenarios and the following keywords (MeSH terms) grouped into arrangements were used: Macular Degeneration OR Age-Related Maculopathies AND Ophthalmoscopy AND Fluorescein Angiography AND Tomography, Optical Coherence AND Antioxidants OR Vitamin E AND Photosensitizing Agents AND Angiogenesis Modulating Agents AND Antibodies, Monoclonal AND Anti-Bacterial Agents.

Degree of recommendation and strength of evidence
A: Experimental or observational studies of higher consistency.
B: Experimental or observational studies of lesser consistency.
C: Case Reports (non-controlled studies).
D: Opinions without critical evaluation, based on consensus, physiological studies, or animal models.

Objective
To evaluate specific questions regarding the methods of examination, diagnosis, and treatment of age-related macular degeneration, resulting from evidence-based clinical practice.

Introduction

Age-related macular degeneration (AMD), or age-related maculopathy, is a degenerative disease that affects the central portion of the retina (macula). It is the most common cause of visual impairment and may lead to loss of central vision or blindness, affecting individuals older than 50 years[1] (**A**). In the early stages of age-related maculopathy, patients may be asymptomatic; however, in its advanced forms the disease may cause serious central vision dysfunction.

Although histologically the retina is a complex, multifaceted structure, a simpler approach is to consider it functionally divided into two parts: a functional entity consisting of a photosensitive layer of rods and cones and their neural connections that collect light and convert it into nervous electrical impulses transmitted through the optic nerve; the other part is the retinal pigment epithelium and its underlying basal lamina (Bruch's membrane), which together maintain the integrity of the barrier between the choroid and the retina. The choroid, which is primarily a vascular tunic, is sandwiched between the retina and the sclera, and is the main source of blood supply to the outer half of the retina.

The pathophysiology of age-related maculopathy is characterized by degenerative alterations involving the outer retina, pigment epithelium, and Bruch's membrane[2] (**D**). With advancing age, the pigment epithelium cells become less efficient, thus the retina can no longer receive adequate nutrients and waste accumulates, leading to deposits called amorphous drusen. Thus, the cells of the retinal pigment membrane slowly degenerate, resulting in central vision loss. This form of slowly progressive disease is called dry type AMD.

Alternatively, if the integrity of the Bruch's membrane is lost, choroidal neovascular complexes grow in the epithelial and subretinal spaces, in a process called choroidal neovascularization[3](**D**). The new blood vessels are fragile and incompetent, allowing for leakage and bleeding, and therefore leading to edema, which compromises the integrity of the retina, the macula, and the fovea, and progressively impairs visual function. The final result is a dense fibrovascular scar, which can involve the entire macular area[4](**C**). This form of the disease is called exudative or wet type AMD, accounting for 90% of cases of severe vision loss in the elderly.

AMD is a multifactorial disease of unknown etiology. Several risk factors are known, among which age is the strongest[5,6](**A**). Ocular risk factors include the presence of soft drusen, macular pigmentary alterations, and choroidal neovascularization in the other eye. Systemic risk factors include hypertension, smoking, and positive family history[7,8](**A**)[9](**D**).

The most common AMD symptoms are central vision blurring, metamorphopsia (image distortion), and reduced vision, which may lead to central scotoma and significant vision loss. Ophthalmoscopic fundus examination shows dry type irregular chorioretinal atrophy and exudative macular edema, often associated with retinal hemorrhages and lipid exudates around the macula.

1. What examination is necessary for the initial diagnosis of age-related macular degeneration?

The fundus examination with dilated pupils (fundoscopy, retinal mapping, or biomicroscopic fundus) is the recommended initial approach for AMD diagnosis. A common condition related to aging and of unknown cause, the disease has varied symptoms and may be asymptomatic in the early stages. Only one eye may have reduced visual acuity, whereas the other may maintain good vision for many years. When both eyes are affected, the loss of central vision is perceived early. It is recommended for all patients aged 55 years or older to determine the risk of developing the more severe forms of the disease[10](**A**).

Recommendation

Fundus examination with dilated pupils is recommended for the initial diagnosis of AMD.

2. For the diagnosis and follow-up of exudative age-related macular degeneration, should only fluorescein angiography be performed, or optical coherence tomography as well?

Fluorescein angiography is an examination that consists of the intravenous administration of a contrast, fluorescein (a non-toxic and highly fluorescent molecule). It allows for the study of the characteristics of blood flow in the retina and choroid vessels, recording details of the pigment epithelium and retinal circulation, as well as providing evaluation of its functional integrity. Optical coherence tomography (OCT) is a diagnostic procedure that uses light to obtain and create an image of the retina and optic disc. Using a technique known as low-coherence interferometry for optical measurements, OCT's principle of operation is similar to that of ultrasound, using light instead of sound. The scanner light is focused on the retina, and the computer analyzes the amount of reflected light, thereby creating an image of the analyzed tissue, previously only possible in histological studies.

When exudative AMD is suspected, it is recommended to perform at least fluorescein angiography and, whenever possible, OCT. The **sensitivity** of each of these tests to detect macular edema of different etiologies is high, and the **correlation** between them is good (sensitivity of 96.1% and 98.7% for OCT and fluorescein angiography, respectively)[11](**B**). However, some discrepancy is found between the methods, as subtle edemas are identified only by fluorescein angiography, with no corresponding alteration detected in retinal thickness by OCT (3.86% of cases of macular disease are observed only by fluorescein angiography)[11](**B**).

Recommendation

Both fluorescein angiography and OCT have high sensitivity, with good correlation to detect macular diseases. However, there is a small chance that, when used alone, they may not detect subtle cases of macular disease.

3. Should all patients older than 65 years, in the presence of drusen and pigmentary alterations in the macular region be treated with minerals and antioxidants to prevent maculopathy progression to the exudative forms and prevent loss > 15 letters in the ETDRS eye chart?

It has been suggested that the disease progression may be decreased in individuals who eat a diet rich in antioxidant vitamins (carotenoids, vitamins C and E) and minerals (zinc and selenium). Oxidative damage to the retina may be related to the pathogenesis of AMD, because the retina, due to its high oxygen concentration and intense light exposure, is susceptible to damage by oxidative stress[12](**D**). Patients with age-related maculopathy of the non-exudative type have different probabilities of progressing to the exudative forms or of having maculopathy-related visual acuity loss.

A multicenter randomized clinical trial designed to evaluate the effect of high doses of zinc, selected antioxidant vitamins (among which, vitamins E, C, and beta carotene administered at 5 to 15 times the recommended daily dose), and zinc supplements in the development of advanced forms of age-related maculopathy in elderly patients (55 to 80 years old), showed that patients in category 2 (extensive small drusen, pigmentary alterations, non-extensive intermediate drusen) showed a probability of only 1.3% of progressing to advanced forms of disease after five years of follow-up.

Patients in category 3 (extensive intermediate drusen, large drusen or non-central geographic atrophy), had an estimated probability of 18% (ranging from 6% in patients with extensive intermediate drusen, up to 27% in those with large drusen and/or extrafoveal geographic atrophy). Patients in category 4 (patients with age-related maculopathy advanced in one eye or loss of visual acuity in one eye related with non-exudative type maculopathy) had a probability of around 43% of progression in five years. Therefore, categorizing patients in groups is important to determine the risk of maculopathy progression and of visual acuity deterioration[10,13](**A**).

In patients classified in categories 3 and 4, the use of vitamins and minerals (500 mg vitamin C, 400 IU vitamin E, 15 mg beta-carotene, 80 mg zinc, and 2.0 mg copper) prevented loss of vision (15 letters in the ETDRS eye chart), demonstrating RRR = 21% with 95% CI: 3% to 38%, and NNT = 17 (95% CI: 9-17). There was also a reduction in the risk of progression to more advanced forms of age-related maculopathy (RRR = 29% with 95% CI: 11% to 46% and NNT = 12 (95% CI: 8-33)[10](**A**).

Recommendation

Only patients classified as belonging to category 3 (extensive intermediate drusen, large drusen or non-central geographic atrophy), especially those who have at least three factors in the simplified severity scale (presence of large drusen or pigmentary alterations or extensive intermediate drusen in both eyes) and category 4 (patients with advanced age-related maculopathy in one eye or loss of visual acuity in one eye related to non-exudative maculopathy) should be treated with antioxidants and zinc. Patients in the lower categories should be followed and treated if they progress to higher severity categories.

4. What are the side effects of antioxidant and zinc use in the treatment of age-related maculopathy and what are the contraindications?

The main potential side effects are kidney stones associated with vitamin C, fatigue, muscle weakness, decreased thyroid function, increased risk of hemorrhagic stroke associated with vitamin E, increased risk of developing lung cancer in smokers, and yellowing of the skin, associated with beta carotene, anemia, decreased HDL, gastric discomfort caused by zinc; in patients that use antioxidants, the main complaint observed was yellowing of skin, when compared to the control group (8.3% *versus* 6%, respectively)[10](**A**).There was a significant increase in hospital admissions due to genitourinary tract diseases in individuals who received zinc supplementation (11.1% *versus* 7.6%, p = 0.0003)[14](**A**).

Recommendation

When treating patients, it is the physician's responsibility to explain the nature of supplementation and the potential side effects caused by long-term use and, especially, the contraindication to the use of beta-carotene in smokers, and vitamin E in diabetic patients with vasculopathies[15](**A**).

5. What is the benefit of using intravitreal ranibizumab in the treatment of neovascular age-related macular degeneration?

Although the physiopathological mechanism is not fully established, evidence suggests that the vascular endothelial growth factor, VEGF-A, is an important mediator involved in the angiogenesis and vascular permeability alterations in neovascular AMD (wet or exudative type)[16,17](**C**). Numerous anti-VEGF molecules, with ranibizumab among them, have been developed in order to limit the deleterious effects of choroidal neovascular formation associated with AMD, mainly by reducing the permeability of new abnormal vessels, as well as reducing the rate of neovascular progression (growth), which often lead to loss of central vision in the affected eye. Ranibizumab, an antibody fragment of recombinant humanized monoclonal anti-vascular endothelial growth factor for intravitreal use, has been extensively studied in several clinical trials, which evaluated its safety and benefit, using different dosages and treatment regimens for that purpose[18-21](**A**).

In another clinical trial, including several centers with a 24-months duration, patients with neovascular AMD and minimally classic lesions or some component of hidden choroidal neovascularization (CNV) without angiographic evidence of classic CNV were randomized to treatment with intravitreal ranibizumab, at monthly doses of 0.3 mg or 0.5 mg, compared to monthly sham injections. After 12 months of treatment, patients treated monthly with intravitreal ranibizumab (0.3 mg and 0.5 mg) showed less loss of visual acuity compared to those who received sham injections (94.5% of patients receiving 0.3 mg of ranibizumab and 94.6% of those receiving 0.5 mg had lost up to 15 letters, at the evaluation through the ETDRS eye chart of basal visual acuity, when compared to 62.2% of those who received the sham injection [p < 0.001])[18](**A**).

The beneficial results regarding visual acuity at 12 months were maintained with continued treatment at 24 months - 92% of patients that received 0.3 mg of ranibizumab, and 90% of those receiving 0.5 mg had lost up to 15 letters (ETDRS eye chart) of basal visual acuity, when compared to 52.9% of those who received the sham injection (p < 0.001)[18](**A**). Regarding ocular adverse events in patients submitted to monthly treatment with intravitreal ranibizumab during the analysis period of 24 months, uveitis was reported in 1.3%, presumed endophthalmitis (negative culture in 4 of 5 cases) in 1.0%, retinal tear in 0.4%, and vitreous hemorrhage in 0.4%; vitreous hemorrhage was observed in 0.8% of patients who underwent sham intravitreal injection, and rhegmatogenous retinal detachment in 0.4%[18](**A**). In a multicenter clinical trial with a 24-month duration, patients with neovascular AMD and predominantly classic lesions were randomized to treatment with monthly intravitreal injections of ranibizumab at doses of 0.3 mg or 0.5 mg (both

associated with sham verteporfin photodynamic therapy) or treatment with photodynamic therapy with active verteporfin (associated with sham intravitreal injections).

After a period of 12 months, patients treated with monthly ranibizumab intravitreal injections (0.3 mg and 0.5 mg) presented less loss of visual acuity compared to those undergoing photodynamic therapy with verteporfin. 94.3% of patients receiving 0.3 mg of ranibizumab and 96.4% of those receiving 0.5 mg of ranibizumab showed loss of up to 15 letters (ETDRS eye chart) of basal visual acuity compared to 64.3% of those undergoing photodynamic therapy with verteporfin ($p < 0.001$)[19,20](**A**). Regarding ocular adverse events in the same period, the following were identified in patients undergoing intravitreal ranibizumab: uveitis in 0.4%, rhegmatogenous retinal detachment in 0.4%, and vitreous hemorrhage in 0.4%. Rhegmatogenous retinal detachment was observed in 0.7% of patients undergoing photodynamic therapy with verteporfin[19](**A**). In both clinical trials[19,20](**A**), all participants completed the 25-item National Eye Institute visual function questionnaire (NEI VFQ-25) at baseline and after 24 months.

In the clinical trial including patients with neovascular AMD lesions and minimally classic lesions or some component of occult CNV with no angiographic evidence of classic CNV, those treated with doses of 0.3 mg and 0.5 mg of intravitreal ranibizumab had a mean score of improvement in the visual function questionnaire of +5.2 (95% CI: +3.5 to +6.9) and +5.6 (95% CI: +3.9 to +7.4) points, respectively, at the end of the first year of treatment. In contrast, patients submitted to sham intravitreal injections had a mean score of -2.8 (95% CI: -4.6 to -1.1) points in the same period, and this difference was significant, favoring the use of intravitreal ranibizumab[22](**A**). In a clinical trial including patients with neovascular AMD and predominantly classic lesions, treated with doses of 0.3 mg and 0.5 mg of intravitreal ranibizumab associated with photodynamic therapy with verteporfin, there was improvement in the mean score of the visual function questionnaire of +5.9 (95% CI: +3.6 to +8.3) and +8.1 (95% CI: +5.3 to +10.8) points, respectively, at the end of the first year of treatment.

In contrast, patients treated with verteporfin photodynamic therapy had a mean score of +2.2 (95% CI: -0.3 to +4.7) points in the same period, and this difference was significant, favoring the use of intravitreal ranibizumab[23](**A**). At each visit up to 24 months, patients treated with intravitreal ranibizumab showed greater chances of improvement in most subscales, including pre-specified ones (near activities, distance activities, and vision-specific dependency).

Recommendation

Based on the results obtained in multicenter randomized controlled trials, the angiogenic drug modulation (or anti-angiogenic therapy or vascular endothelial growth antifactor therapy) with ranibizumab, via intravitreal application for a period of two years in patients with AMD showed significant improvement in visual acuity, with low rates of adverse events.

6. When should treatment of neovascular age-related macular degeneration with intravitreal ranibizumab be started?

In order to obtain favorable results concerning visual acuity, efforts should be made in order to shorten the time from diagnostic confirmation to the start the angiogenic drug modulation with intravitreal ranibizumab, since neovascular choroid lesions (subfoveal) can progress rapidly, at an average rate of approximately 10 micrometers per day[24,25](**C**).

In multicenter clinical trial lasting 24 months, patients with neovascular AMD lesions, minimally classic or with some component of occult CNV, and with no angiographic evidence of classic CNV, were randomized to treatment with intravitreal ranibizumab at monthly doses of 0.3 mg or 0.5 mg, compared to monthly sham injections. After 12 and 24 months, approximately 1/4 of the patients treated with 0.3 mg ranibizumab and 1/3 of the patients treated with 0.5 mg showed gains of 15 or more letters (ETDRS eye chart) of visual acuity compared with 5% or less of patients undergoing sham injections ($p < 0.001$)[18](**A**). The administration of ranibizumab (0.3 mg and 0.5 mg) resulted in visual acuity improvement within the first seven days after use, while visual acuity in patients submitted to sham injections showed decline over the follow-up period[18](**A**).

Another multicenter randomized clinical trial observed, soon after the first month of follow-up, poor visual acuity in patients submitted to sham injections, when compared to those receiving ranibizumab doses of 0.3 mg and 0.5 mg[26](**A**).

Recommendation

Angiogenic drug modulation with intravitreal ranibizumab for the treatment of neovascular AMD must be initiated as soon as possible, preferably within a period of one month after diagnosis confirmation, respecting obvious limitations inherent to the treatment process, such as obtaining the relatively high-cost medication.

7. Is the use of topical antibiotics before each treatment session (intravitreal injection) mandatory?

Recent advances in the treatment of retinal diseases have made intravitreal injections an increasingly common route of drug administration. However, this procedure is not risk-free, and endophthalmitis is one of the most serious complications, with reported incidences ranging from 0.02% to 1.9% per injection[27,28](**C**). Other complications described include retinal detachment and acute cataracts[29](**A**). Since endophthalmitis is a devastating complication, ocular surface preparation prior to the procedure remains controversial, but it has been acknowledged in a prospective study that the use of topical 5% povidone-iodine preoperatively reduces the risk of endophthalmitis after intraocular procedure[30](**B**).

A clinical trial reported the incidence of endophthalmitis after intravitreal drug administration using a standardized protocol that required topical povidone-iodine and sterile blepharostat, but did not require the use of gloves or sterile drapes or use of topical antibiotics (before, on the same day, or after intravitreal injection procedure). Topical antibiotics were used on the day of administration in 9.4% of 3,838 intravitreal injections, for several days after the administration in 21.2%, and on the day of administration, as well as after, in 36.2%. In the remaining 1,276 intravitreal injections (33.3%), topical antibiotics were not used. Three cases of endophthalmitis were observed, confirmed by culture after intravitreal ranibizumab injection (0.09%), and all cases had used antibiotics for several days after the intravitreal procedure[31](**A**).

Recommendation

The results suggest that a low rate of endophthalmitis can be attained by applying a protocol that includes the use of topical povidone-iodine, sterile blepharostat, and topical anesthesia, without the need of topical antibiotics, gloves, and sterile drapes.

Conflict of interest

Costa RA has received honorariums for lectures in a scientific activity program sponsored by Novartis. Meirelles R has received reimbursement for attending a symposium sponsored by Novartis.

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