GUIDELINES OF CLINICAL PRACTICE OF THE SERV: TREATMENT OF EXUDATIVE AGE-RELATED MACULAR DEGENERATION (AMD)

GUÍAS DE PRÁCTICA CLÍNICA DE LA SERV: TRATAMIENTO DE LA DEGENERACIÓN MACULAR ASOCIADA A LA EDAD (DMAE) EXUDATIVA

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ABSTRACT

Objective: Age related macular degeneration (ARMD) in its neovascular form is a serious disease which produces legal blindness in many patients with poor prognosis if left untreated. We intend to establish a clinical guide with the different therapeutic options that exist nowadays, which may help the ophthalmologists in their clinical practice.

Methods: A group of medical retina experts selected by SERV have evaluated the results of different published studies with the drugs currently available, obtaining an evidence-based consensus. Some recommendations have been established for diagno-

RESUMEN

Objetivo: La Degeneración Macular Asociada a la Edad (DMAE) en su forma húmeda supone una grave enfermedad que condiciona ceguera legal en muchos pacientes y con mal pronóstico si no es tratada. Pretendemos establecer una guía de actuación clínica con las diferentes opciones terapéuticas que existen en el momento actual, que puedan ayudar al oftalmólogo en su práctica clínica.

Métodos: Un grupo de expertos en retina médica seleccionados por la SERV han evaluado los resultados de diferentes estudios publicados con los fármacos actualmente disponibles, llegando a un...
DEVELOPMENT OF THE GUIDE

1. Definition of objectives

The objective of the neovascular ARMD Treatment Guide is to provide a reference tool for ophthalmologists/retinologists to facilitate the management of patients affected by this disease in their daily clinical practice, based on current scientific knowledge.

As all health professionals, the authors have the final objective of improving the quality of life of our patients by means of improving the diagnostic, treatment and rehabilitation to achieve the best possible visual acuity.

The authors have offered consensus in what concerns the current outlook about the benefits and risks of current treatment strategies.

2. Clinical scenarios in which the Guide can be applied

The disease which is the focus of this guide is Age Related Macular Degeneration (ARMD) of the exudative type. The target population is comprised by patients aged 50 or over.

3. Methods

A search has been carried out among scientific publications in relation to the object of this guide to base the therapeutic recommendations on scientific knowledge.

The scientific information we utilized is derived from different levels of evidence. The highest evidence is that based on multicentre, randomized and controlled cynical trials or by a meta-analysis study...
of non-randomized controlled clinical trials. In this group we can also include published analyses of cases and controls with an adequate design. The lowest level of evidence is provided by descriptive studies, presentations of case reports and the viewpoint of experts expressed in scientific literature.

4. Consensus method utilized for formulating recommendations

The meeting of the working group facilitated consensus by all members as regards the recommendations included in this guide.

5. Validation of the guide

This guide was validated by the SERV (Spanish Retina and Vitreous Society).

6. Validation by external agents

This guide was validated by the following reviewers:
- Alfaro, Virgil (United States).
- Saravia, Mario (Argentina).
- Corcóstegui Guraya, Borja (Spain).
- Piñero Bustamante, Antonio (Spain).

ARMD MANAGEMENT SCHEME

Atrophic ARMD

1. Symptoms

- Progressive visual acuity loss.
- Difficulty reading
- Metamorphopsia.

2. Clinical symptoms

Eye fundus findings:
- Hard drusen: yellowish and well defined deep retinal lesions, representing the earliest stage of atrophic ARMD.

ARMD management algorithms.
– Soft drusen: yellowish retinal lesions with edges not as defined as hard drusen and of a larger size.
– Drusenoid RPE detachment: it only amounts to the coalescence of soft drusen which sometimes simulates the form of an RPE detachment.
– Pigment accumulations: these accumulations indicate more severe lesions and can be frequently seen adjacent to the soft drusen.
– Calcified drusen: soft drusen in reabsorption stage due to partial degeneration of the RPE cells located above them.
– RPE atrophy: The final stage of this form of the disease which is reached when the RPE cells above the drusen degenerate.

3. Special tests

The atrophic ARMD diagnostic is made on the basis of a biomicroscopical exploration of the retina. The identification of any sign described above is sufficient to establish the diagnostic. Only in the cases with drusen-like RPE detachments it is advisable to discard the presence of a choroidal neovascular membrane. To this end, fluorescein angiography (FAG) as well as Optical Coherence Tomography (OCT) would be useful. Some authors recommend indocyanine Green angiography in these cases to discard a hidden choroidal neovascular membrane.

4. Differential diagnostic

It must be established with diseases that course with drusen or that produce atrophies in the choriocapillary RPE, Including dystrophies such as dominant autosomic drusen or central areolar atrophy.

5. Treatment

In the earliest stages of the disease it is not necessary to initiate any specific treatment although a diet rich in zeaxantine and lutein is recommended. These pigments are generally present in fruit and vegetables and in higher concentrations in spinach, watercress, broccoli, corn, oranges and egg yolks. Zeaxantine and lutein supplements seem to increase the concentration of these pigments in the macula increasing its resistance against free radicals. An additional dieting recommendation is blue fish and dried fruits (nuts) due to their high content in long chain polyunsaturated fatty acids of the omega-3 family. Of these, docosahexaenoic acid (DHA) seems to be most directly involved in the prevention of age related retinal lesions.

When the eye fundus reveals the presence of large soft drusen (>125 microns = the thickness of a vein in the optic nerve edge) and pigmentary alterations, the risk of development towards advanced stages of ARMD is high. Therefore, it is recommended to begin treatment with antioxidant vitamins (vitamin E, C and beta carotenes) as well as

ALGORITHM 2
Treatment guidelines for atrophic ARMD

<table>
<thead>
<tr>
<th>Bilateral soft drusen exceeding 125 µ with or without pigmentary alteration</th>
<th>Drusen in contralateral eye to exudative ARMD or severe atrophy of RPE</th>
</tr>
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<tbody>
<tr>
<td>Antioxidants</td>
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mineral supplements (zinc). However, none of the drugs approved in our country has dosages as high as those utilized in clinical trials which have proven that, even though these substances do not prevent the disease, they could reduce the rate of progression towards its advanced forms and visual loss (AREDS). Perhaps the response to supplements in the AREDS study are not uniform in all patients and are related to the CFH genotype (supplement factor H).

These vitamin supplements are also indicated for patients who ready exhibit severe ARMD in one eye, both the exudative and the atrophic type, regardless of the size of the drusen in the less affected eye because the risk of progression is high.

It is important to emphasize that the high dosages of antioxidant vitamins and minerals are not free of risk. For example, vitamins with beta-carotene (pro vitamin A) must not be administered to smokers or former smokers who kicked the habit less than eight years ago because it increases the risk of lung cancer. Vitamin E increases the risk of heart failure in patients with vascular diseases, while zinc can produce intestinal disorders.

At this time there is no treatment that has proved significant clinical efficiency with the ability to improve or halt the progression of the disease in this type of ARMD.

Exudative ARMD

1. Symptoms

– Sudden and progressive loss of visual acuity
– Central scotoma.
– Difficulty reading.
– Metamorphopsia.
– Photopsiae.

2. Clinic

Findings in the macular area:
– Exudative retinal detachment.
– Serous detachment of retinal pigmentary epithelium.
– Intraretinal hemorrhage.
– Subretinal hemorrhage.
– Sub-RPE hemorrhage.
– Lipidic exudates.

Classification of the choroidal neovascular membranes according to location:
– Subfoveal, affecting the centre of the fovea.
– Juxtafoveal, between 1 and 200 microns from the centre of the fovea.
– Extrafoveal, over 200 microns from the centre of the fovea.
– Juxtapapillary, adjacent to the optic disc.

Classification of neovascular membranes according to angiographic behavior:
– Predominantly classical. Membranes with cartwheel pattern with an extension exceeding 50% the size of the lesion.
– Minimally classical. Membranes with cartwheel pattern with an extension under 50% the size of the lesion.
– Hidden. No typical cartwheel pattern is evidenced. They can appear as late hyper-fluorescence of indeterminate origin or as the fibrovascular detachment of the RPE.

Hidden membranes that have obtained their own identity:
– RAP (Retinal Angiomatous Proliferation). Neovascular disease which begins as intraretinal and later extend to the subretinal space to establish retina-choroid anastomosis. Indocyanine green angiography is a useful tool for diagnosing this disease.
– Idiopathic polypoid choroidal vasculopathy. Polypoid vascular dilatations in the choroids associated to repeated subretinal bleeding conditions. Best evidenced with indocyanine green angiography.

3. Special tests

Fluorescein angiography (FA)

The classification of neovascular membranes according to their radiographic behavior was very important in the past because the results with thermal laser and photodynamic therapy differed according to the different types of membranes. Nowadays we have anti-VEGF pharmacological treatments which allow a visual acuity improvement of 1/3 of patients with exudative ARMD,
regardless of the type of memory. It is not necessary either to perform an angiography to assess the response to treatment because generally retreatment criteria are based on visual acuity, OCT findings and ocular fundus biomicroscopy exploration.

However, it is advisable to perform at least a fluorescein angiography at the time of diagnostic because it is useful as a prognostic. Classical membranes are much more aggressive than the hidden ones. The treatment of a hidden membrane could be delayed when it does not exhibit signs of activity such as visual acuity loss or bleeding, while the treatment of a classical membrane cannot be delayed because the risk of progression and visual loss is much greater.

Angiography with indocyanine Green (AIG)

This type of angiographic study continues to be utilized in the study of hidden neovascular membranes, above all for the identification of the typical patterns of idiopathic polypoid choroidal vasculopathy (IPCV) and retinal angiomatous proliferation (RAP).

Optical coherence tomography

This is the par excellence test for studying exudative ARMD. It allows for a quantitative analysis of activity signs and the response to treatment. In addition, it is a fast and non-invasive test, in contrast with fluorescein or indocyanine green angiography. It is very useful not only for diagnosing the disease but also for the subsequent follow up, particularly after treatment with intravitreal antiangiogenic injections. By means of OCT we can detect increases in the thickness of the retina with the presence of fluid, which could appear even weeks before the patient notices any symptom (loss of visual acuity, increase of metamorphopsia).

4. Differential Diagnostic

To be established with diseases coursing with exudative retinal detachment in the macular area, with intra- or sub-retinal bleeding or a deep lipidic exudation. Among these, the main are:

- Central serous choroidopathy in patients over 50.
- long-term retinal venous and vascular occlusions.
- Juxtafoveal telangiectasias.
- Sub-retinal bleeding due to macroaneurysms or tumors.

5. Treatment: anti-VEGF drugs

At present, the most efficient treatment is pharmacological with anti-vascular endothelial growth factor (VEGF), which is one of the most important factors involved in angiogenic stimuli.

Available drugs:

- Ranibizumab (Lucentis®). Variable fraction of the anti-VEGF antibody.
- Bevacizumab (Avastin®). Full anti-VEGF antibody.
- Sodic Pegaptanib (Macugen®). Aptamere against VEGF isoform 165.

These drugs are delivered through the intravitreal pathway by means of injections which must be administered regularly because their mean life is short. At present research is in progress for finding several delayed release systems in order to maintain more stable intravitreal levels and avoid frequent injections.

Although clinical trials have proved the efficiency of this type of therapy (Lucentis® : ANCHOR and MARINA; Macugen® : VISION), intravitreal injections are administered every 30 or 45 days and at present the tendency is to space out the injections because in most cases they must be maintained for years.

**ARMD TREATMENT SCHEME**

**Treatment of exudative ARMD**

**Laser photocoagulation**

Laser photocoagulation can be utilized in well defined classical lesions at extrafoveal and juxtafoveal locations. We must bear in mind the
high rate of relapses (close to 50%) and the risk of irreversible scotoma. For this reason and even though there are no scientific data on the results of the use of intra-vitreous anti-angiogenic injections in juxtafoveal lesions, many authors prefer to utilize drugs having anti-angiogenic capacity (1-3). We could also consider this mode of treatment for peri-papillary lesions (4) and for treating IPCV (5) and RAPs (6), in which we can utilize it with or without associated intravitreal triamcinolone injection (7).

**Surgery**

In the course of time, vitrectomy has reduced its indications for this disease. At present, the most frequent ones are massive sub macular hemorrhages as a complication of the exudative form (8) and some juxta-papillary neovascular membranes the extension of which does not affect the foveal avascular area (9).

**Photodynamic therapy**

The use of verteporfin (Visudyne®) combined with red wavelength laser stimulation facilitates an improvement of the natural evolution of subfoveal lesions with classical component greater than 50% of the lesion and a total diameter smaller than 5,400 microns. Association with intravitreal triamcinolone injection improves the results (10-14).

In these situations, the foreseeable result is loss of vision (15,16) and therefore, vis-à-vis the results obtained with new therapeutic options, PDT should not be considered nowadays as the treatment of choice and should be taken into account only when it is impossible to apply anti-angiogenic intravitreal treatment.
The combination of anti-angiogenics and PDT seems to reduce the number of required intravitreous injections but the visual results are not as good as with anti-angiogenic treatment (19,20).

### Ranibizumab

The intravitreous injection of ranibizumab (Lucentis®) at a dosage of 0.5 mg allows significant visual acuity improvements in subfoveal lesions according to the data obtained in studies with the highest level of evidence. It should be considered as the drug of first choice due to the scientific qualification of results supporting it (21-28).

The efficiency and safety of ranibizumab was first assessed in the two year-long MARINA study which compared the drug with placebo in hidden or minimally classic lesions. The patients included in the study were randomized to receive one of the two dosages of ranibizumab, 0.3 mg or 0.5 mg, or a simulated injection once a month for 24 months. After 12 months, 95% of patients that had received ranibizumab lost under 15 ETDRS letters (3 ETDRS lines), against 62% of patients who were treated with simulation injections (P<0.001). In addition, 25% of patients treated with 0.3 mg of ranibizumab and 34% of patients treated with 0.5 mg of ranibizumab gained 15 letters or more of visual acuity, compared to 5% of patients in the control group (P<0.001). These improvements were sustained at two years. For the first time in history of subfoveal exudative ARMD treatments, the evolution of the mean visual acuity of treated patients tended towards improvement. In what concerns adverse effects, there was 1% of endophthalmitis and 1.3% of uveitis.

Subsequently, the 2-year long ANCHOR study, comparing ranibizumab against PDT in predominantly classic lesions yielded very similar results. The patients included in the study were randomized to receive one of the two doses of ranibizumab, 0.3 mg or 0.5 mg, every month or photodynamic therapy every three months according to the criteria established for this treatment for a 24-month period. At month 12, between 94% and 96% of patients that were given ranibizumab lost under 15 ETDRS letters (a moderate loss of vision) in comparison with 64% of patients that received photodynamic therapy (P<0.001). in

### Pegaptanib sodium

The use of pegaptanib sodium (Macugen®) for intra-vitreous injection with a dose of 0.3 mg as a treatment for active subfoveal lesions with a total size smaller than 12 disc areas with a neovascular component exceeding 50% of the lesion allows for results similar to PDT but in a broader range of neovascular lesions (17).

The probability of obtaining significant eyesight improvements is low (6%). Therefore, pegaptanib should be used as a second line of treatment in cases where ranibizumab is contraindicated or the patient rejects the treatment. Its advantage vis-à-vis PDT is that pegaptanib can be utilized for all types of lesions, whereas photodynamic therapy can be used for the above-mentioned ones (17,18).

**ARMD management algorithms.**

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**ALGORITHM 4**

**Exusative ARMD treatment guidelines**

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>Treatment of relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-angiogenics (charge dosage)</td>
<td>Antiangiogenics (maximum monthly frequency)</td>
</tr>
<tr>
<td>Monthly injection for three months</td>
<td>Criteria:</td>
</tr>
<tr>
<td></td>
<td>▪ Intra- or subretinal hemorrhage</td>
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<tr>
<td></td>
<td>▪ Subretinal liquid</td>
</tr>
<tr>
<td></td>
<td>▪ Retinal thickening over 100 μ</td>
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<tr>
<td></td>
<td>▪ Visual acuity loss of one line</td>
</tr>
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<td></td>
<td>▪ New membrane</td>
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**ARMD management algorithms.**
addition, 36% of patients that received 0.3 mg of ranibizumab and 40% of patients that received 0.5 mg of ranibizumab gained 15 or more ETDRS letters of vision, compared to only 6% of patients had received photodynamic therapy. Just as in the MARINA study, the mean visual acuity of treated patients also tended towards improvement. Adverse effects, such as endophthalmitis and uveitis, remained under 1%.

**Bevacizumab**

Bevacizumab is not a drug approved for intraocular use or for treating neovascular ARMD. However, the accumulated experience after treating thousands of patients in recent years and the results of multiple series published in high impact journals demonstrated that bevacizumab (Avastin®) can provide benefits closer to the results obtained with ranibizumab than those obtained with photodynamic therapy and pegaptanib (29-40). These are two very efficient drugs, one approved for intra-ocular use and indicated for neovascular ARMD, demonstrated in clinical trials, and the other without approval for intraocular use or indication for ARMD and demonstrated in a multiple series of patients. For this reason, we believe that, according to current scientific evidence, ranibizumab should be the first choice above bevacizumab.

In the cases that do not fulfill the inclusion criteria for which ranibizumab was approved and for which authorization for use can be obtained according to current legislation, bevacizumab could be a good option.

We cannot forget that the annual cost of treatment with bevacizumab is well below that of Bevacizumab, and this could facilitate providing treatment to a higher number of patients for socioeconomic reasons.

**«Starting» dosages**

According to the results obtained in the MARINA and ANCHOR studies with ranibizumab, the utilization of three consecutive injections at 4-week intervals yields the best results in terms of visual acuity improvements. After this sequence, the evolution curve begins to flatten (21,22).

Therefore, the recommendation for the «initial» or «starting» dosage is as mentioned above, i.e., 3 consecutive intravitreal interactions. However, we must consider the possibility that the three dosages may not be necessary. This will depend on the specialists judgment in particular situations.

In the treatment chapter of the neovascular ARMD document, the reader can review fully detailed results of the published studies which justify said algorithm.

**Post-treatment follow up**

After treating exudative ARMD with the chosen procedure, it is time to best follow up because any of the therapeutic choices involves a strict control of the patient with a scheme adapted to the applied treatment. This is important because the disease exhibits a high number of relapses with any one of the selected options.

Depending on the chosen treatment, the algorithm will be different but will always involve the execution of all or some of the following tests at the specialist’s criterion: visual acuity measurements in identical conditions throughout the follow-up, if possible utilizing ETDRS optotypes, macula biomicroscopy with contact or non-contact lenses, FAG and OCT.

Fifteen days after photocoagulation with thermal laser we must check the patient including FAG. This check shall be repeated between four and six weeks according to the criterion established by the ophthalmologist depending on the ocular fundus findings (1,2,41).
When the therapeutic treatment was PDT verteporfin, the recommended interval is of three months for two years, also including FAG. The results of the TAP/VIP studies do not determine whether the application of PDT at intervals below 10 weeks in patients with active disease could yield a benefit.

After intra-vitreous injection of Macugen®, the follow-up will be established at six week intervals (17,18). When the product utilized was Lucentis®, we must check the patient every four weeks (21,22). The same periodicity must be applied when we have utilized Avastin® (32,35). In these cases, the information provided by OCT will allow us on many occasions to avoid FAG. We can always fall back on this procedure in the presence of diagnostic doubts about the existence of neovascular activity.

In any case, it is up to the ophthalmologist’s criterion on the basis of the data arising from the patient’s exploration to decide which tests are necessary and which can be skipped at each checkup visit.

In the case of intra-vitreous injection with anti-angiogenics, the highest levels of efficacy (MARINA and ANCHOR studies) were obtained with monthly injections of ranibizumab during a two-year period (21,22). This is not very feasible in daily clinical practice and therefore it is suggested to consider the possibility of reducing the number of injections (42,43). To this end, retreatment criteria were established on the basis of findings allowing for the identification of a relapse or the persistence of neovascular activity because the findings published with fixed retreatment criteria did not provide good visual results (43).

The PRONTO study utilized the loss of five ETDRS letters associated to fluid in the macula detected by OCT, an increase of GCR of at least 100 microns, the appearance of a new classic NVC or macular hemorrhage or persistence of fluid detected by OCT at least one month after the previous injection (42).

This approach involves one checkup visit by the patient every four weeks and the application of a new injection in the presence of the above-mentioned criteria. According to the type and aggressiveness of the lesion, after three checkups without neovascular activity we may consider prolonging the checkup periodicity on a case-by-case basis. Up to at least one year without active disease the checkups should not be separated by three months or more. To do this, we must instruct the patient to detect as early as possible the symptoms of a relapse with self-examinations of monocular vision in the affected eye. If vision is reduced or new metamorphopsia appears or an existing one increases in size (Amsler’s grid is very helpful for detecting these changes in the patient), an appointment with the ophthalmologist must be made as soon as possible.

When the patient’s “first eye” is affected, we must warn him about the bilateral nature of the disease, explaining that the atrophic form tends to become bilateral and symmetric with a progression/growth rate of 1/10 papillary diameter per year. In the neovascular form the rate of growth is of about 10 µm/day with a tendency towards bilaterality, i.e., the risk for the second eye is of: the first year, 4%; the second year, 10%; the third year 17%; and approximately 25% the fifth year.

In these circumstances, the patient must be aware of the importance of an early diagnostic in the second eye and therefore visit the practice urgently if experiencing any reduction in vision or changes in the metamorphopsia. For this purpose, Amsler’s grid can be useful.

REFERENCES


