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SAVRS Guidelines for the Management of Neovascular Age-Related Macular Degeneration

This is a revised Clinical Practice Guideline – Reviewed May 2024 (Dr BN Gundry)

Main Changes:

- Update in treatment regime / medication
- Re-formatting of article in accordance with new OSSA guidelines for society document publications

Key Points:

- Clinical examination
- Diagnostic tests
- Intravitreal therapy

Scope and purpose:

- To describe the management of Neovascular Age Related Macular Degeneration (nAMD)
- To discuss the available anti-VEGF treatments currently licenced in South Africa
- The guideline applies to health professionals and funders

Stakeholder involvement:

- The guideline development group includes individuals from the SAVRS Academic Advisory Committee (AAC)
- The AAC includes Ophthalmologists from both the public and private sector

Editorial Independence:

- No funding or sponsorship was received for the publication of this clinical guideline
- The views of medical aids, government bodies and manufacturers of therapeutic agents have not influenced the content of this guideline
- No competing interests from guideline development group members were present

Adoption of recommendations from other guidelines:

- Recommendations were added to the existing guidelines (Drs Acton et al) due to the addition of more anti-VEGF agents licenced in South Africa as well as the introduction of a new imaging modality (OCT-angiography). We have used international “best practice” of a treat and extend protocol in these guidelines.

Evidence-based methods:

- A systematic internet search for evidence on the management of nAMD was performed
- Evidence was selected based on peer reviewed publications and guidelines from international ophthalmology groups[1,2]
- There is an explicit link between the recommendations and the supporting evidence
- The guideline has been externally reviewed by the SAVRS Academic Advisory Committee

- Suggested future complete document revision: 2029

The Academic Advisory Committee (AAC) of the South African Vitreoretinal Society (SAVRS) would like to update the guidelines for the management of exudative/neovascular age-related macular degeneration (nAMD). The committee would like to record the following points:

1. Age-related macular degeneration (AMD) is the leading cause of irreversible visual loss in patients over the age of 65 years. It is a chronic condition that requires life-long management. AMD is a PMB condition. (ICD-10 H35.3; 904B in the Council of Medical Schemes PMB coded list of 2013).
2. The Council for Medical Schemes PMB ICD-10 codes list (dated 2013) still lists nAMD under "retinal detachment, tear and other retinal disorders" (H35.3) with the diagnosis-and-treatment-pair options listed as "vitrectomy; laser treatment; other surgery." The current international standard of care for the treatment of nAMD is the regular injection of intra-vitreal anti-VEGF agents. The paired treatment options in the PMB list are therefore outdated and no longer valid. Ophthalmologists are required by the HPCSA to offer current international standard of care to their patients. To offer outdated care would make them medicolegally liable. Therefore, this document aims to provide updated guidelines for the management of nAMD to ophthalmologists and funders.
3. Anti-VEGF monotherapy is the standard of care for the management of nAMD (level I evidence). Treatment guidelines are detailed in Appendix 1.
4. The following anti-VEGF agents are currently scientifically validated, and registered locally and internationally for the treatment of nAMD:
   a) Ranibizumab (Lucentis®)
   b) Aflibercept (Eylea®)
   c) Brolucizumab (Vsiqq®)
   d) Faricimab (Vabysmo®)
5. Bevacizumab (Avastin®) carries international registration and MCC registration for the treatment of carcinoma of the colon but is NOT registered for use in the eye. The use of Bevacizumab (Avastin®) for the management of nAMD is therefore in an "off-label" capacity. This is despite evidence that equates its efficacy and safety profile to Ranibizumab (Lucentis®). The SAVRS would like to emphasize that although Bevacizumab (Avastin®) is widely used for the treatment of nAMD due to its lower price, the decision to use Bevacizumab (Avastin®) is often dictated by funding/funders and may not be the first choice of the treating ophthalmologist.
6. Bevacizumab (Avastin®) is packaged as a single, sterile vial for use as an intravenous agent. The fluid content of each vial is commonly compounded into multiple smaller quantities to lower the unit cost for intravitreal injections. Ideally, compounding pharmacies prepare the units under strict aseptic conditions. The SAVRS recommends that compounding is performed by an experienced operator under sterile conditions such as an operating theatre or under a laminar flow hood suitable for preparation of sterile intravenous medication. Compounding costs are expected to vary amongst centers according to different usage patterns, facility costs and other economic determinants.
7. Some funders have not consulted the appropriate South African specialist opinion (SAVRS), but have used nAMD treatment guidelines from other countries, specifically the United Kingdom National Institute for Health and Care Excellence (NICE) guidelines. These guidelines, although comprehensive and excellent, do not include Bevacizumab (Avastin®) as a treatment option since the UK national health system (NHS) does not authorize the use of Bevacizumab (Avastin®) for intraocular use. Hence, these guidelines are not directly applicable to a South African context.

APPENDIX 1: Recommended treatment for nAMD

1. Patients should be referred to a suitably trained ophthalmologist for diagnosis and management.
2. The diagnosis of nAMD should be confirmed by the ophthalmologist and baseline visual acuity should be recorded. There are no visual acuity exclusions for treatment.
3. A fundus fluorescein angiogram (FFA) of the eye may be required to confirm the diagnosis. Indications to repeat an FFA include failure to respond to treatment and worsening of visual acuity. FFAs are performed at a hospital or at the doctor's rooms depending on the ophthalmologist's preference and the availability of emergency resuscitation facilities. Indocyanine green angiography (ICG) may be indicated to investigate patients who do not respond to treatment and in suspected atypical cases such as polypoidal choroidal vasculopathy (PCV).
4. The optical coherence tomography (OCT) scan is a pivotal investigation for the diagnosis and follow-up of nAMD. OCT should be performed (as a minimum) at baseline, at month 3 after initiation of therapy (although scans during the loading phase are extremely helpful in assessing response and predicting further treatment patterns) , and when clinical history or examination suggests disease activity. OCT Angiography (OCTA) is a new modality which may add valuable information when conventional OCT and FFA are equivocal as to the presence of a choroidal neovascular membrane.
5. The standard of care is initial intravitreal injections of a single anti-VEGF agent, either 0.5mg Ranibizumab (Lucentis®), 2.0mg Aflibercept (Eylea®), 1.25mg Bevacizumab (Avastin®) or 6.0mg Faricimab (Vabysmo®). 6.0mg Brolucizumab (Vsiqq®) is recommended as a second line agent. Brolucizumab (Vsiqq®) use is in uveïtic patients (previous intra-ocular inflammation) is contraindicated. Brolucizumab also has a higher risk of causing intraocular inflammation and occlusive vasculitis than the other available drugs.
6. Intravitreal injections should be performed in a suitable aseptic environment, either in a hospital setting or in the doctor's rooms, at the discretion of the treating ophthalmologist.
7. Treatment is initiated with a loading dose of 3 monthly (or as close to this as logistically possible) intravitreal injections, irrespective of the agent used. The response to treatment is then reassessed and monthly injections are continued until there is no disease activity or no reasonable prognosis for vision stabilization or improvement. Once the disease is inactive ("dry" retina on OCT), further treatment and follow-up intervals depend on the choice of regimen used by the ophthalmologist. Current "real world" experience is that a "treat and extend" regimen provides the best possible visual outcomes with the lowest burden of treatment for the patient. See Appendix 2 below for details on this treatment method. Patients still require regular re-assessments with an ophthalmic examination and OCT (FFA may be necessary when OCT results equivocal) to determine the appropriate interval between injections as well as to assess the ongoing efficacy of the chosen anti VEGF agent.
8. Non-responders to the initial choice of anti-VEGF agent will require alternative treatments. These include changing to a different anti-VEGF agent or using combination strategies such as a combination of an anti-VEGF agent with Visudyne photodynamic therapy (PDT).
9. Certain sub-types of nAMD require special consideration. These sub-types require additional treatment modalities besides anti-VEGF monotherapy. When available, Visudyne photodynamic therapy (PDT) in combination with anti- VEGF therapy may be indicated for nAMD secondary to idiopathic polypoidal choroidal vasculopathy (PCV) or retinal angiomatous proliferation (RAP).

APPENDIX 2: Treat and extend protocol

1. The patient would receive an injection at each visit.
2. After an initial loading phase of 3 or more monthly (or as close to monthly as logistically possible) the interval between injections is extended by 2 weeks provided the OCT (retinal anatomy) disease inactivity and the patient's visual acuity is improved.
3. The maximum extension will depend on the anti VEGF used and its expected duration of action.
4. Upon presence of disease recurrence evidenced by visual acuity changes or worsening anatomical parameters (fluid on OCT or subretinal blood on fundus imaging) the interval is extended by 2 weeks (at each subsequent visit) until the disease is stabilized. Once it has stabilized it is try extend again although one may use shorter extension intervals to reduce the chance of recurrence.
5. The treat and extend protocol seek to extend or reduce the interval in between injections interval for each individual patient evidenced by stable vision and retinal anatomy. It reduces the unrealistic burden of monthly visits whilst still maintaining good visual acuity
6. Most patients would require fewer injections over time (i.e. longer intervals in between treatments)

PLEASE NOTE THAT WHEN SWITCHING FROM ONE AGENT TO ANOTHER DUE TO TREATMENT FAILURE ONE MAY NOT ALWAYS REVERT BACK TO A LOADING DOSE PHASE-THIS DECISION WILL DIFFER IN EACH CLINICAL SCENARIO AND THE TREATING PHYSICIAN WILL DECIDE BASED ON EXPERIENCE WITH THE "FAILED" DRUG AND THE PREVIOUS TREATMENT INTERVALS.

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