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

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 The paired treatment options in the PMB list are therefore outdated and no longer valid.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 To offer outdated care would make them medicolegally liable.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 mAMD 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®) – Note that for this guideline, Aflibercept (Eylea®) has been called an anti-VEGF agent, although its mechanism of action (VEGF trap) differs slightly from the other anti-VEGF agents mentioned.
    c) Brolucizumab (Vsiqq®)
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. In South Africa, where no compounding pharmacies exist, the pharmacists or ophthalmologist needs to perform the

compounding process themselves. 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 centres 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 subfoveal 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, and when clinical history or examination suggests disease activity.
5. The standard of care is initial intravitreal injections of a single anti-VEGF agent, either 0.5mg Ranibizumab (Lucentis®), Aflibercept (Eylea®), or 1.25mg Bevacizumab (Avastin®). Brolucizumab (Vsiqq®) is recommended as a second line agent and its use is cautioned in uveitic patients (previous intra-ocular inflammation) or where bilateral injections are indicated.
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 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, further treatment and follow-up intervals depend on the choice of regimen used by the ophthalmologist. Current level 1 evidence show that the best visual outcomes are achieved with ongoing monthly intravitreal injections. Alternate treatment regimens include the "treat-and-extend" regimen and the PRN dosing schedule. Whilst both alternate regimens aim to reduce the burden of monthly injections, they still require regular re-assessments with an ophthalmic examination and OCT and repeat injections whenever there is any decrease in vision or evidence of disease activity. Brolucizumab (Vsiqq®) is specifically registered as an 8-12 weekly injection after the initial 3x monthly loading dose.
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).

References:

1. Abraham P, et al. Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-Related Macular Degeneration: PIER Study Year 2. Am J Ophthalmol. 2010; 150: 315-324.
2. Abell et al. Intravitreal injections: is there benefit for a theatre setting? Br J Ophthalmol 2012; 96: 1474-1478.
3. Amoaku WM et al. Defining response to anti-VEGF therapies in neovascular AMD. Eye 2015; 29: 721-731
4. Allen C, et al. Twenty-four-Month Efficacy and Safety of 0.5 mg or 2.0 mg Ranibizumab in Patients with Subfoveal Neovascular Age-Related Macular Degeneration. Ophthalmology 2014; 121: 2181-2192.
5. Arnold JJ, et al. Two-Year Outcomes of "Treat and Extend" Intravitreal Therapy for Neovascular Age-Related Macular Degeneration. Ophthalmology 2015; 122:1212-1219.
6. Berg K, et al. Comparison of Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration According to LUCAS Treat-and-Extend Protocol. Ophthalmology 2015; 122: 146-152.
7. Brown DM, et al. Ranibizumab versus Verteporfin Photodynamic Therapy for Neovascular Age Related Macular Degeneration: Two-Year Results of the ANCHOR Study. Ophthalmology 2009 116:57-65.
8. Chakravarthy U, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet 2013;12;382:1258-1267.
9. Gupta OP, et al. A Treat and Extend Regimen Using Ranibizumab for Neovascular Age-Related Macular Degeneration. Ophthalmology 2010;117:2134-2140.
10. Holz FG, et al. Safety and Efficacy of a Flexible Dosing Regimen of Ranibizumab in Neovascular Age-Related Macular Degeneration: The SUSTAIN Study. Ophthalmology 2011; 118:663-671.
11. Lalwani GA, et al. A Variable-dosing Regimen with Intravitreal Ranibizumab for Neovascular Age related Macular Degeneration: Year 2 of the PrONTO Study. Am J Ophthalmol 2009; 148:43-58
12. Lally DR et al. Preferred therapies for neovascular age-related macular degeneration. Curr Opin Ophthalmol 2012; 23: 182-1884
13. Maguire MG, et al. Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration. Ophthalmology 2016;123:1751-61.
14. Martin DF, et al. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-Related Macular Degeneration: 2-Year Results: Comparison of Age-related Macular Degeneration Treatments Trials. Ophthalmology 2012; 119(7):1388-98.
15. Oubraham H, et al. Inject and extend dosing versus dosing as needed. Retina 2011; 31:26-30.
16. Royal College of Ophthalmologists. Age related Macular Degeneration: Guidelines for Management. September 2013 and 2021.
17. Schmidt-Erfurth U et al. Guidelines for the Management of Neovascular Age-Related Macular Degeneration by TH European Society of Retina Specialists (EURETINA). Br J Ophthalmol 2014; 98: 1144-1167.
18. Silva R et al. The SECURE Study: Long-Term Safety of Ranibizumab 0.5 mg in Neovascular Age related Macular Degeneration. Ophthalmology 2013; 120:130-139.
19. Toalster N, et al. A 12-month prospective trial of inject and extend regimen for ranibizumab treatment of age-related macular degeneration. Retina 2013; 33:1351-1358.
20. Wykoff CC, et al. Prospective Trial of Treat-and-Extend versus Monthly Dosing for Neovascular Age-Related Macular Degeneration. Ophthalmology 2015; 122: 2514-22.
21. Dugel PU, et al; HAWK and HARRIER Study Investigators. HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration. Ophthalmology. 2020 Jan;127(1):72-84. doi: 10.1016/j.ophtha.2019.04.017. Epub 2019 Apr 12. PMID: 30986442.
22. NICE guidelines: (23 January 2018) www.nice.org.uk/guidance/ng82

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