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SAVRS Clinical Practice Guideline for the management of Diabetic Maculopathy

This is a revised Clinical Practice Guideline – Reviewed June 2024 (Dr E Albrecht).

Main Changes:

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

Key Points:

- Clinical classification
- Diagnostic tests
- Intravitreal therapy options

Scope and purpose:

- To describe the work-up and management of Diabetic Macular Oedema (DMO).
- To discuss the indications/options for intravitreal therapy in DMO.
- 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 adopted from the following existing international guidelines

- **The Royal College of Ophthalmologists** – Clinical guidelines, Diabetic Maculopathy Diabetic Retinopathy Guidelines Dec 2012[3].
- **American Academy of Ophthalmology** – Diabetic Macular Edema: Diagnosis and Management May 2021[2]
- **American Society of Retinal Specialists** - Evidence-Based guidelines for Management of Diabetic Macular Edema 2019[1]
- **Euretina**: Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists April 2017[4,5]
- European School for Advanced Studies in Ophthalmology (**ESASO**) classification and staging of Diabetic Macular Edema[6.]

Evidence-based methods:

- A systematic internet search (google scholar) for evidence on the management of DMO was performed.
- Evidence was selected based on peer reviewed publications and guidelines from international ophthalmology groups. 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.

CLINICAL ASPECTS and KEY RECOMMENDATIONS

Background:

- Diabetes Mellitus (DM) remains a growing global challenge and is a PMB condition (Treatment pair 31K – medical management). Any routine examination of a diabetic patient to exclude diabetic eye disease or diabetic related complications is therefore also a PMB condition (ICD-10: E10.3 or E10.9; E11.3 or E11.9)
- Diabetic Macular Oedema (DMO) is the most common cause of vision impairment in diabetic patients. The prevalence is reported from 3.8% (USA) to between 12.5-20% in certain settings in South Africa. The majority of patients are in the working age group and the disease, as well as the frequency of the treatment options, has significant impact on the work environment.
- DMO is a chronic condition that requires life-long management. DMO is a PMB condition. (ICD-10 E10.3/H36.0/H36.2/H35.3 or E11.3/H36.0/H36.2/H35.3; 904B in the Council of Medical Schemes PMB coded list of 2013).
- The Council for Medical Schemes PMB ICD-10 codes list (dated 2013) still lists DMO 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 DMO is the regular injection of intra-vitreal anti-VEGF agents. The paired treatment options in the PMB list are therefore outdated and vitrectomy and laser treatment are an option for selected cases with very specific clinical findings. 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 DMO to ophthalmologists and funders.
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Associations and risk factors

- The important risk factors in the management of DMO:
  - Hemoglucosetest (Hgt) or blood sugar control - best monitored by 3-4 monthly glycosylated hemoglobin (HbA1C) and daily glucose monitoring.
  - Blood pressure control, cholesterol risk profile and renal impairment are important factors as well.

- The most common ocular association of DMO is diabetic retinopathy as DMO can occur during non-proliferative as well as proliferative diabetic retinopathy.

- Diabetes is a well-known risk factor for all forms of vasculopathies such as heart attacks, strokes, nephropathy, peripheral vascular disease and this association/risk can be a factor in the treatment algorithm.

Diagnosis

The initial examination of a patient with suspected DMO includes all relevant aspects of the comprehensive adult medical eye evaluation, with particular attention to those aspects related to retinal vascular disease as well as glaucoma and cataract. The patients' medical history regarding other systemic diseases is also relevant.

- **Diagnostic tests**

  A number of imaging tests may enhance the clinical examination and optimize patient care. The most common tests include the following:

  - ***Optical coherence tomography (OCT)***

    - Provides high-resolution imaging of the macula and is the main stay of confirming DMO. Although there are numerous classification systems for DMO – the most simple classification uses OCT to classify:
      - **No DMO**
      - **Non-CIDMO:** Non-Center Involved/Non Foveal Involving DMO. Macular oedema is present, but not involving or threatening the central 1mm central foveal area.
      - **CIDMO:** Center-Involving/Foveal Involving DMO
        Macular oedema present and affecting the central 1mm foveal area.

    - Important morphological biomarkers to note:
      - Central subfoveal thickness
      - Intra-retinal cysts
      - Hyperreflective foci
      - Subretinal fluid
      - Vitreomacular interface abnormalities
      - Disrupted retinal inner layers (DRILL)
      - Integrity of External Limiting Membrane and Ellipsoid Zone

    - OCT Based DMO can then be staged into
      - **Stage 1: Early** DMO (10-30% thickening and no outer retinal changes)
      - **Stage 2: Advanced** DMO (severe cystic swelling >30% swelling with minimal outer retinal changes)
      - **Stage 3: Severe** DMO (severe swelling with outer retinal changes)
      - **Stage 4: Atrophic** (retinal atrophy with poor identification of outer layers)

- ***Optical Coherence Tomography Angiography (OCTA)***
  - OCTA uses non-dye based evaluation of the retinal blood vessels and is useful in DMO to show both the morphological parameters as well as the status of the fine blood vessels. It can be particularly useful to show any macular ischemia, which can affect the treatment outcome.

- ***Fluorescein angiography (FA)***
  - FA evaluates the extent of the vascular damage by the Diabetes, confirms the leakage into the macular, can highlight the leaking micro-aneurysms prior to laser therapy, can show macular ischemia and can highlight the diabetic retinopathy status, especially proliferative retinopathy with neovascularization.

Management (General)

- All diabetic patients require optimization of their vascular risk factors; Hgt, Blood Pressure, Cholesterol risk, Renal impairment and this may require assistance of their G.P., Dietician, Physician or Endocrinologist.

- A Comprehensive Eye evaluation and OCT scan should be able to classify most patients into 4 clinical scenarios:

  - **Non-CIDMO**:

    - No oedema present or threatening the central macular area.
    - The Early Treatment Diabetic Retinopathy Study (EDTRS) showed that laser therapy, appropriately applied reduced the risk of visual loss by 50% and remains a treatment option if required.
    - Both Micropulse laser and Argon laser are validated options.

  - **CI-DMO with preserved Visual Acuity:**

    - Oedema of central subfoveal area, but Best Corrected Visual Acuity (BCVA) is 6/7.5 or better.
    - These patients were traditionally excluded from major trials.
    - Recent data from Diabetic Retinopathy Clinical Research group Protocol V[7] evaluated this group comparing **Laser**, anti-Vascular Endothelial Growth Factor (**anti-VEGF)** injections and 3 monthly **observations**. Results suggested that there was no significant difference at 2 years if any treatment option was delayed until vision or OCT worsened.
    - The treating Ophthalmologist will need to carefully discuss the treatment options and personalize the therapy according to the patients' requirements.

  - **CI-DMO with reduced Visual Acuity**:

    - Oedema of central subfoveal area and the BCVA is less than 6/7.5.
    - The current gold standard is intravitreal anti-VEGF therapy. Initial loading usually consists of 4-6 monthly injections. Studies have repeatedly shown that in the first year of therapy most patients require intensive treatment, typically 8-9 injections and then less in subsequent years.

- Alternative option of first line intravitreal steroid injection may be useful in certain scenarios; pseudophakic patients, evidence of inflammation, systemic risks such as recent heart attacks/strokes or vitrectomised patients.
- With multiple treatment options available, it is important for the treating Ophthalmologist to personalize the treatment option for each patient.

- **<u>CI-DMO due to Traction:</u>**

  - Center involving DMO caused by anterior-posterior traction due to Vitreomacular Traction or due to tangential traction from an epiretinal membrane may require a Pars Plana Vitrectomy with epiretinal membrane (ERM) and / or internal limiting membrane (ILM) peeling by a Vitreo-Retinal surgeon.
  - The post op residual oedema may benefit from intravitreal treatment with anti-VEGF or steroids.

Intravitreal injections

- Anti-Vascular Endothelial Growth Factor **(Anti-VEGF)**

  Currently, four anti-VEGF agents are available for treatment of DMO:
  - Bevacizumab (Avastin®) remains off-label for ophthalmologic conditions, although widely used.
  - Ranibizumab (Lucentis®) approved by the FDA and SAHPRA
  - Aflibercept (Eylea®) approved by the FDA and SAHPRA.
  - Faricimab (Vabysmo®) has been approved by the FDA and recently by SAHPRA
  - Aflibercept 8mg High Dose (Eylea HD®) has been approved by FDA and is expected in the RSA market in the very near future.

- **Corticosteroids**

  - Dexamethasone implant (Ozurdex®) has been approved by the FDA and SAHPRA for the treatment of diabetic macular oedema.
  - Preservative free Triamcinolone is used off label, although evidence demonstrating its efficacy also exists.
  - The side effect profile for corticosteroids differ from anti-VEGF's, with an increased risk of cataract formation and intra ocular pressure (IOP) rise.
  - Recent description of Suprachroidal Injection of steroid seems promising, potentially alleviating the risk of cataract and IOP elevation.

TREATMENT PROTOCOLS FOR INTRAVITREAL TREATMENT OF DMO

- Treatment of risk factors (to be managed by the patient's physician/G.P./Endocrinologist/Dietician)

Initiation of Therapy/Loading

- Most Anti-VEFG agents require 3-6 monthly injections as a loading phase

- At follow up, if response is *sufficient* and vision/OCT morphology shows stability (no change over 2 consecutive visits) then the options are to inject on a as needed (PRN) basis or to use the treat and extend protocol.
- In the PRN regime, the patient is reviewed every 3-4 months and injected as required.
- In the Treat/Extend Protocol; the patient is injected and the follow up is extended by 2-4 weeks and if stable, injected again and follow up extended by an additional by 2-4 weeks.

Switching to Alternative agent

- If the response to the initial anti-VEGF agent is insufficient then there is quality evidence (DRCR.net Protocol AC[8]) that switching to an alternative agent is beneficial.
- Second Line agent can either be an alternative anti-VEGF, preferably with a different mechanism of action (Aflibercep [VEGF Trap], Faricimab [anti-VEGFA + Angio 2]) or a different class such as steroids (dexamethasone or triamcinolone).
- If intravitreal steroids are used then the patient will require follow up to assess the intra-ocular response, intra-ocular pressure and review max response at 6-8 weeks, then again at approx. 4 months to see if the treatment needs to be repeated. Ozurdex® seldom lasts 6 months as initially thought.

Maintenance

- Most DMO patients will require intensive therapy in the first year and then less in subsequent years.
- Evidence from studies suggest a mean no of 15 injections is required in the first 2 years and then subsequently less.
- Evidence from long term follow up studies (OLE and ENDURANCE trials[9]) suggest that only 25 % of patients will not have recurrence of DMO requiring treatment, with most patients still requiring 3 injections annually through years 4-5.
- It is important for all parties to be aware of the chronicity of the disease.
- The latest longer acting anti-VEGF agents (Faricimab and Alfibercept 8mg HD) and the longer acting Dexamethasone add significant durability benefit, which should be considered especially in the economically active patients as the 3-4 monthly treatment intervals reduces the treatment burden for the patients significantly. This was highlighted by the NICE statement guidelines on the use of Vabysmo® in the NHS[10].

Completing Treatment

- If the visual acuity and OCT central macular thickness (CMT) returns to normal then the treatment can be stopped and reviewed 3-4 monthly and retreated if needed.
- If the vision and CMT stabilize then treatment can be extended until no further benefit is gained – usually if 2 consecutive visits show similar visual acuity and CMT change of less than 10%.
- Of note: if treatment is completed or stopped then patient needs regular follow up to monitor for progression of diabetic retinopathy to proliferative retinopathy and for recurrence of DMO.

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