Anti-VEGF Recommendation for DME & RVO

A recommendation from Bangladesh Vitreo-Retina Society - BVRS

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CONTENT

Section 1: Disease overview

What is DME & RVO?

DME[1] :

- Diabetic macular edema (DME) describes the accumulation of fluid in the intraretinal layers of the macula as a result of leakage from the retinal microvasculature.
- DME can arise during the course of diabetic retinopathy-a chronic microvascular complication of Type 1 or Type 2 diabetes mellitus and is a leading cause of visual impairment in the diabetic population

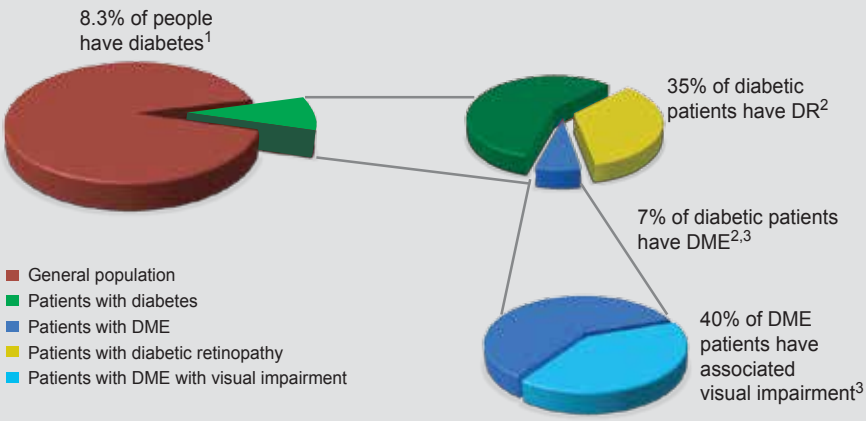
RVO [2,3] :

- Retinal vein occlusion (RVO) describes the narrowing or blockage of a retinal vein, the origins of which are multifactorial. The pathogenic mechanism of RVO is variable, with a host of local and systemic factors acting in different combinations and to different extents to produce the vascular occlusion.
- In general, RVO presents with variable degrees of visual loss with any combination of fundal findings consisting of retinal vascular tortuosity, retinal hemorrhages, cotton wool spots, optic disc swelling and macular edema.

Diabetes and Vision Loss[4-7]

- Diabetes mellitus (DM) is a prevalent disease. Most common complications are microvascular changes[4]
- Diabetic retinopathy (DR) a common microvascular complication of diabetes
- Diabetic Macular Edema (DME) affects approximately 10% of the diabetic population and can develop in both Type 1 and 2 DM[5]
- About 8.3% of Diabetic patients develop DME with visual impairment
- DME is a common cause of blindness in people of a working age[6,7]

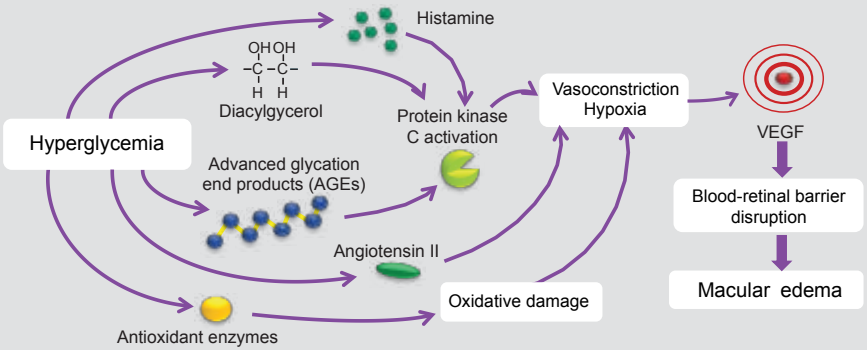
DME is the most prevalent cause of visual impairment in patients with diabetes[8-11]



1. IDF Diabetes Atlas. 5th Edition 2. Yau J et al. Diab Care 2012;35:556-64; 3. Minassian D, et al. Br J Ophthalmol 2012;96:345-9; 4. Stratton IM, et al. Diabetes Care 2013;36:580-5

VEGF is Central of DME pathology[12]

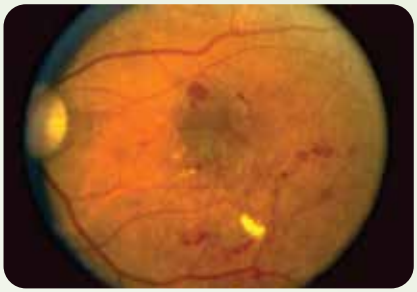
The exact molecular mechanism of vascular disruption is unclear, but several biochemical pathways have been implicated in disease progression

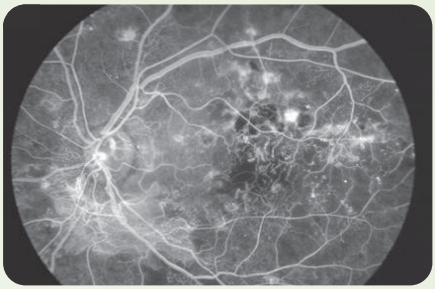


Bhagat N et al. Surv Ophthalmol 2009;54:1-32

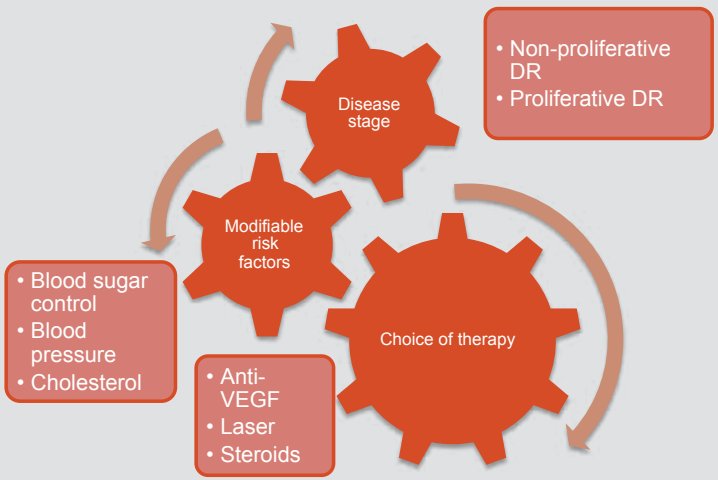
VEGF165 in Diabetic Retinopathy[13]

- Retinal VEGF165 levels elevated in experimental diabetes
- Increased VEGF165 levels found in vitreous of eyes with proliferative DR
- DR patients have higher VEGF165 levels in the aqueous





Factors to consider when treating patients with DME[14]



DME Treatment: Systemic Factor Control[15,16] & Ocular treatment option[17-20]

Systemic Factor Control

Aim- Prevent retinopathy & its progression

1. Blood Glucose Control
2. Blood Pressure Control
3. Blood lipid control

Ocular Treatment Option

Aim- Prevent Vision Loss & Improve vision

1. Anti-VEGF- Improves VA
2. Laser Treatment- Stabilizes vision but rarely restores vision
3. Steroids- Associated with ocular adverse events.
4. Vitrectomy.

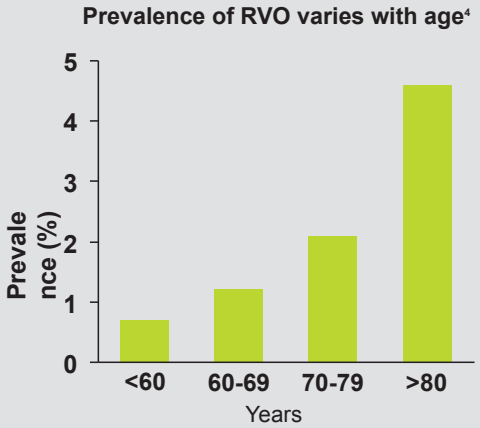
Retinal vein occlusion (RVO)[21-24]

The second most common retinal vascular disorder after diabetic retinopathy[21]

A significant cause of visual impairment[21]

Reduced quality of life and functional activities of daily living[22]

Overall prevalence varies from 0.7% to 1.6%[23,24]



Different types of RVO[25,26]

There are two main types of RVO
- Central (CRVO)
- Branch (BRVO)

BRVO is more common than CRVO
- BRVO, 0.6%–1.1%
- CRVO, 0.1%–0.4%

Pathology[27,28]

- All types of RVO are multifactorial in origin and their pathology includes one or more of the following[27]

  √ Narrowing of the retinal vein due to external pressures
  - sclerotic adjacent structures
  - secondary endothelial proliferation

  √ Primary venous wall disease

  √ Hemodynamic disturbances

- In both CRVO and BRVO, the development of new vessels and macular edema result in variable loss of vision
- In one study, nearly 10% of eyes with BVRO had new vessels present and another 10% had macular edema present[28]

CRVO[29]

- Non-ischemic CRVO

  √ Site of occlusion is distal to the lamina cribrosa or the adjacent retrolaminar region

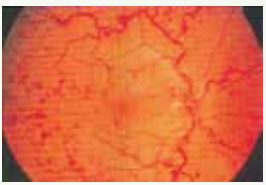
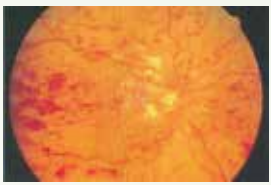
  √ Sluggish retinal circulation due to fall in perfusion pressure resulting from arise in proximal venous pressure

- Ischemic CVRO

  √ Site of occlusion is in the region of the lamina cribrosa (or immediately posterior)

  √ Marked rise in venous pressure

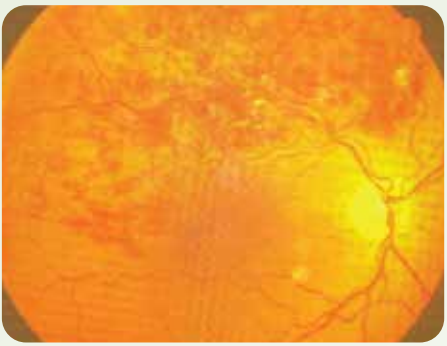
  √ Retinal hemorrhage due to rupture of ischemic capillaries

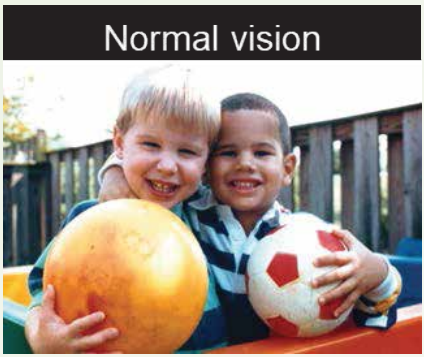



BRVO[30,31]

- Defined by the site of occlusion
  √ Major BVRO (occlusion within one of the major branch retinal veins)
  √ Macular BVRO (occlusion within one of the macular venules)

- Pathogenesis of BRVO may be due to a combination of three primary mechanisms
  √ Compression of the vein at the A/V crossing
  √ Degenerative changes of the vessel wall
  √ Abnormal hematologic factors





VEGF, vascular endothelial growth factor

Summary of treatment for RVO[32]

Interventions for CRVO	Interventions for BRVO
Steroids	Steroids
Thrombolysis	
Intravitreal thrombolysis	
Retinal venous thrombolysis	
Ophthalmic artery thrombolysis	
Isovolemic hemodilution	Isovolemic hemodilution
Radial optic neurotomy	Vitrectomy
Chorioretinal anastamosis	Arteriovenous crossing sheathotomy
Optic nerve sheath decompression	Chorioretinal anastomosis
Lamina puncture (experimental)	Anti-VEGF
Ant-VEGF	

Laser photocoagulation is one of the treatment of choice for neovascularization secondary to RVO.

Section 2: At a Glance few points about Anti-VEGF

What is Anti-VEGF[33]

Anti-VEGF stop the abnormal blood vessels growing, then leaking and bleeding under the retina.

This prevents or limits damage to the retinal light receptors and loss of central vision. These medicines are effective in preventing further central vision loss in up to 90% of treated eyes.

Role of VEGF[34,35]

- Ischemic damage to the retina stimulates increased VEGF* production in the vitreous cavity
- High VEGF levels stimulate
  - √ Neovascularization of the posterior and anterior segments of the eye
  - √ Capillary leakage leading to macular edema

Anti-VEGF procedure of administration[36]

Anti-VEGF procedure of administration:

To prepare the vial for intravitreal administration, please adhere to the following instructions: The vial is for single use only. Anti-VEGF is not licensed for multi-dose, further compounding or vial splitting. Use of more than one injection from the vial can lead to contamination and subsequent infection.

All components are sterile and for single use only. Any component with packaging showing signs of damage or tampering must not be used. The sterility cannot be guaranteed unless the component packaging seal remains intact. Re-use may lead to infection or other illness/injury.

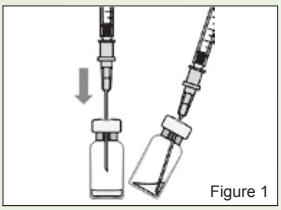


Figure 1

1. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected.
2. Assemble the 5 um filter needle (18 gauge) onto the 1 mL syringe using aseptic technique. Push the blunt filter needle into the center of the vial stopper until the needle touches the bottom edge of the vial.
3. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal (Figure 1).

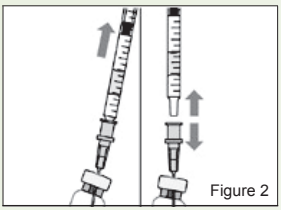


Figure 2

4. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
5. Leave the blunt filter needle in the vial and disconnect the syringe from the blunt filter needle. The filter needle should be discarded after withdrawal of the vial contents and should not be used for the intravitreal injection (Figure 2).

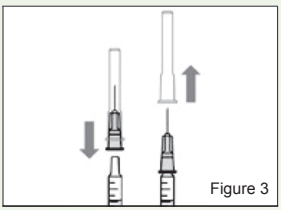


Figure 3

4. Aseptically and firmly assemble the injection needle (30 gauge x ½ inch) onto the syringe.
5. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe (Figure 3).

   Note: grip at the yellow hub of the injection needle while removing the cap.

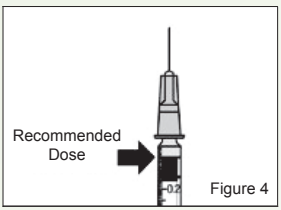


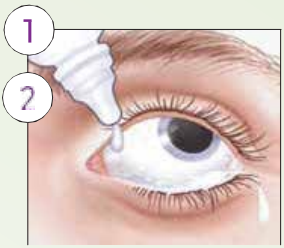
Figure 4

8. Carefully expel the air from the syringe and adjust the dose to the 0.05 mL mark on the syringe (Figure 4). The syringe is ready for injection. Note: do not wipe the injection needle. Do not pull back on the plunger.

   The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the center of the globe. The injection volume of 0.05 mL is then delivered; a different scleral site should be used for subsequent injections.

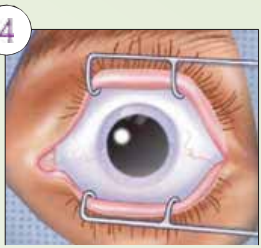
After injection, do not recap the needle or detach it from the syringe. Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.

Preparation of the eye to administer Anti-VEGF[36]

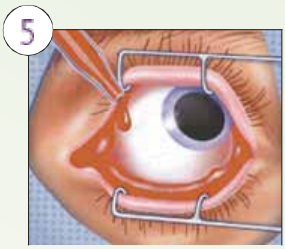


1. Dilate the pupil.
2. Apply topical anesthesia.

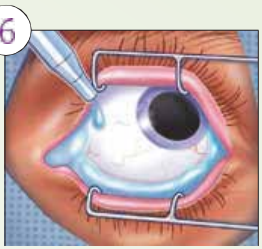
3. Apply 10% povidone iodine solution to periocular skin, lids and eyelashes, and place sterile drape over eye.



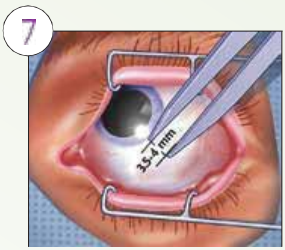
4. Apply sterile eyelid speculum.



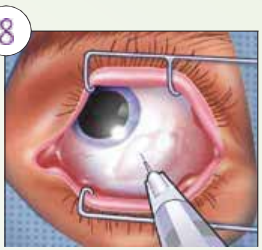
5. Instill 5% povidone iodine ophthalmic solution and wait for 90 seconds.



6. Rinse the eye with ophthalmic saline solution.



7. Direct the patient to look away from the injection site. Mark an injection site at an area 3.5 mm to 4.0 mm posterior to the limbus, avoiding the horizontal meridian.



8. The injection needle should be inserted aiming towards the center of the globe. Slowly deliver the injection volume, then remove the needle slowly. A different scleral site should be used for subsequent injections so that the same site is not injected repeatedly.

Note: prophylactic topical antibiotics according to local clinical practice

General Guidance for Administration[37]

- Anti-VEGF is available as a vial with a filter needle
- Anti-VEGF should be inspected visually for particulate matter and discoloration prior to administration
- The vial is for single use only. Anti-VEGF is not licensed for multi-dose, further compounding or vial splitting. Use of more than one injection from the vial may lead to contamination and subsequent infection
- The injection procedure should be carried out under aseptic conditions:
  > The use of surgical hand disinfection, sterile gloves, a sterile drape and sterile eyelid speculum (or equivalent) is recommended
  > The periocular skin, eyelid and ocular surface should be disinfected
  > Adequate anesthesia and a broad-spectrum topical microbicide should be administered prior to the injection
- Prophylactic topical antibiotics should be used according to local clinical practice
- The patient's medical history should be carefully evaluated for hypersensitivity reactions prior to performing the intravitreal procedure

At a glance general storage guideline for Anti-VEGF[38]

- Need to look in folding box of the drugs for details information.
- Generally in a refrigerator (2°C to 8°C). Do not Freeze
- Keep the vial in the outer carton in order to protect from light
- Prior to use, the unopened vial may be kept at room temperature (25° C) for up to 24 hours. Anti-VEGF should not be used after the date marked “EXP” on the pack
- Anti-VEGF must be kept out of the reach of children.

Anti-VEGF at a glance importance of cold chain[39-41]

The consequences of bad supply chin problems can be potentially life-threatening sometimes.[39]

Medicinal products and, if necessary, healthcare products should be stored separately from other products likely to alter them and should be protected from the harmful effects of light, temperature, moisture and other external factors. Particular attention should be paid to products requiring specific storage conditions.[40]

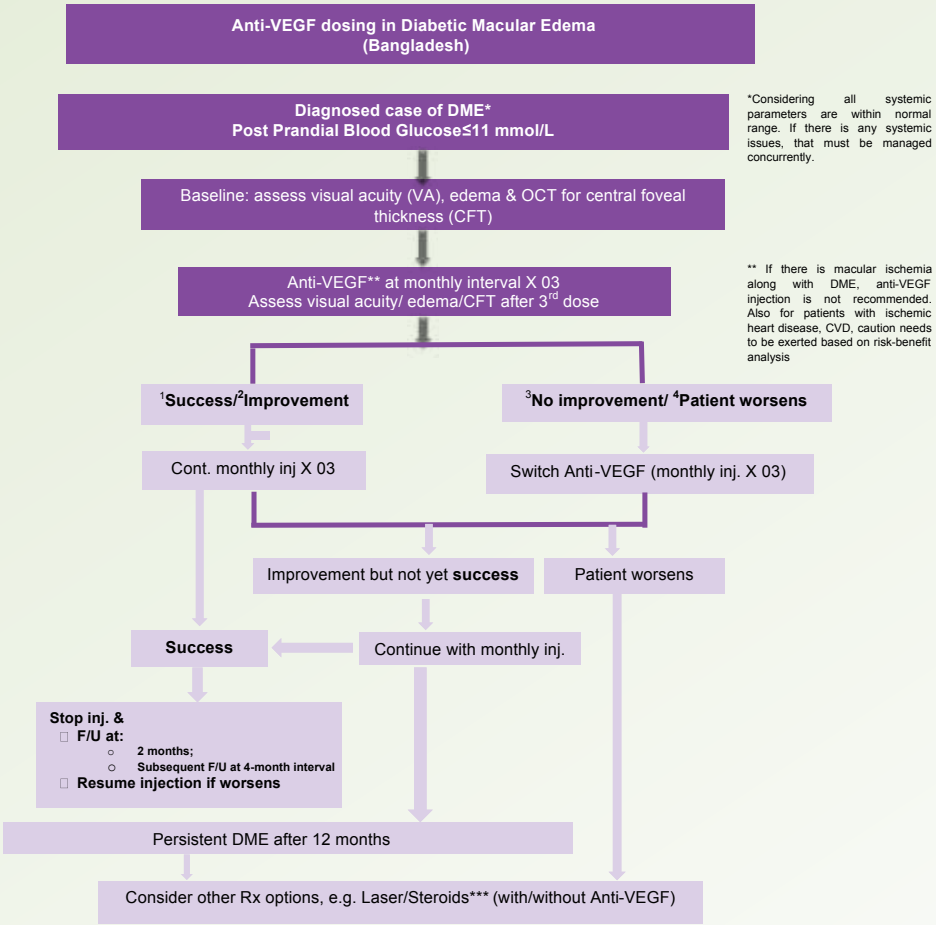
Medicinal products should be handled and stored in such a manner as to prevent spillage, breakage, contamination and mix-ups.[40]

Pharmaceuticals products should be transported using appropriate environment, e.g. using cold chain for thermolabile products. There should be an adequate number of competent personnel involved in all stages of the distribution of pharmaceutical products in order to ensure that the quality of the product is maintained.[41]

Distributors should from time to time conduct risk assessments to assess potential risks to the quality and integrity of pharmaceutical products.[41]

Section 3: Consensus

Consensus for DME



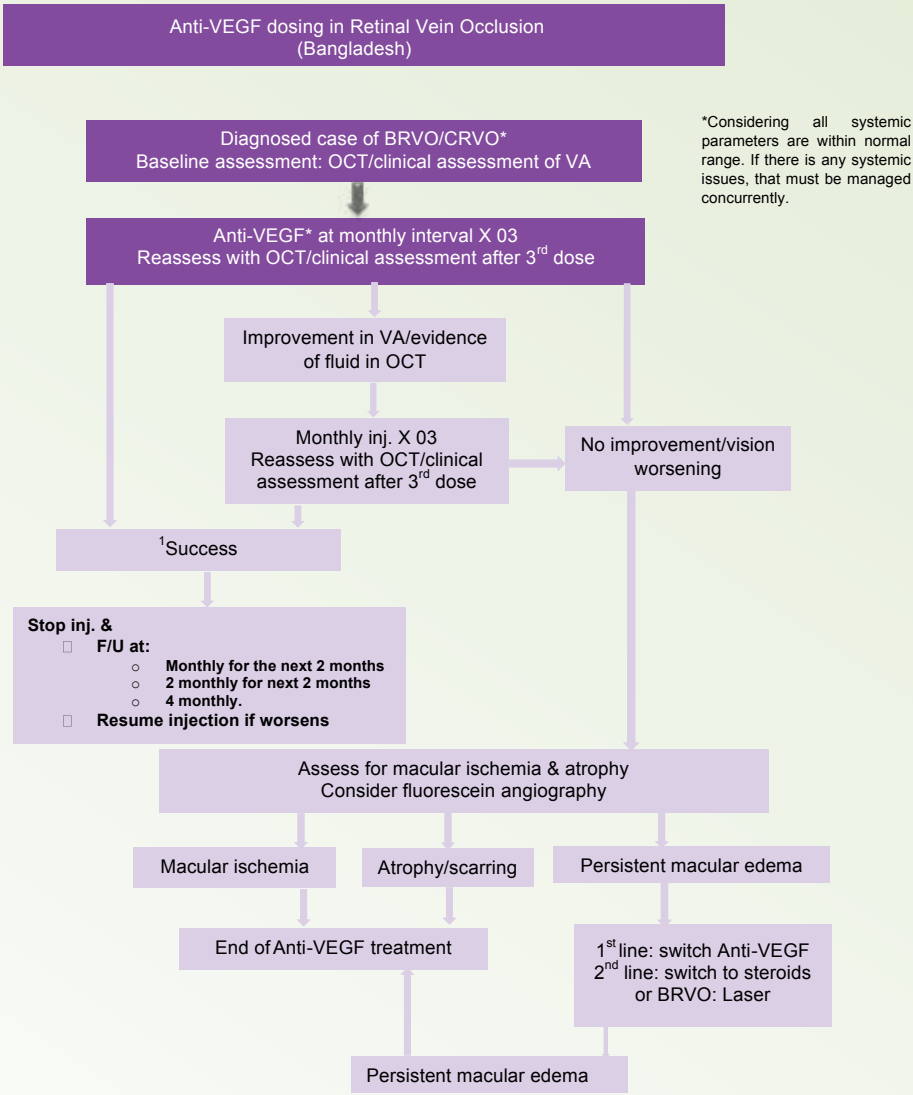
***Intravitreal corticosteroid treatment may be considered as 1st line in certain conditions, e.g. pseudophakic or postvitrectomy eyes, or high risk of thromboembolic events

[1] **Success:** VA (~20/20 or 6/6)/OCT CFT <250 µm.
[2] **Improvement:** Letter gain ≥5 compared to baseline /OCTCFT decreased by ≥10 µm compared to baseline.
[3] **No Improvement:** Letter gain<5; CFT improvement <10 µm
[4] **Patient worsens:** Edema recurs &/or CFT increasing below desired level &/or VA decreasing below desired level).

Note:

1. **Any complication associated with the disease & treatment must be managed accordingly.**
2. **For any patient who attained the success criteria after 1-2 anti-VEGF injections, it is advisable to complete the loading dose to minimize the risk of rebound.**

Consensus for RVO



[1]**Success:** VA>20/40, or OCT >250 µm

Note:

1. **Any complication associated with the disease & treatment must be managed accordingly.**
2. **For any patient who attained the success criteria after 1-2 Anti-VEGF injections, it is advisable to complete the loading dose to minimize the risk of rebound.**

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41. https://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodDistributionPracticesTRS957Annex5.pdf (WHO technical report, NO. 957, 2010, WHO good distribution practices for pharmaceuticals products)

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