

Ranibizumab: The Clinician's Guide to Commencing, Continuing, and Discontinuing Treatment

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The National Institute for Health and Clinical Excellence (NICE) Guidance has recommended ranibizumab in the treatment of wet age related macular degeneration (AMD). The Institute further recommended that a national protocol specifying criteria for discontinuation of ranibizumab is developed. Criteria for discontinuation should include persistent deterioration in visual acuity and identification of anatomical changes in the retina that indicate inadequate response to therapy.

The Royal College of Ophthalmologists (RCOphth) recognised the need for such guidance and brought together a group of clinicians with expertise in the treatment of AMD with ranibizumab, NICE and Department of Health (DH) to develop this guide.

It is confirmed that LogMAR (ETDRS) vision charts, Optical Coherence Tomography (OCT) (OCT 3 or higher specification equivalent), and stereo fundus fluorescein angiography (FFA) are the minimum requirements for adequate AMD service delivery. It is considered inappropriate for a contemporary AMD service to be contemplated without these basic requirements.

When interpreting these guidelines it is important to recognise that clinical variations may occur at each stage in the management of any individual case, and that the decision to commence, re-treat or discontinue therapy rests with the clinician in consultation with the patient.

A. Criteria for commencement of treatment

1. Diagnosis of Active CNV lesion

A diagnosis of choroidal neovascularisation (CNV) should be confirmed by FFA, except in

cases of allergy that preclude this investigation, and OCT (Stratus OCT 3 equivalent or higher specification) before commencement of therapy.

2. Visual Acuity

The Best Corrected Visual acuity (BCVA) should be 6/96 (LogMAR 1.2 or 24 ETDRS letters) or better in the eye to be treated.

3. Structural damage to fovea

It should be established that there is no significant permanent structural damage to the fovea in the eye under investigation before treatment is commenced. Significant structural damage is defined as longstanding fibrosis or atrophy in the fovea, or a significant chronic disciform scar which, in the opinion of the treating clinician, would prevent the patient from deriving any functional benefit (i.e. prevent further loss of vision) from treatment.

4. Recent progression of lesion

CNV disease progression is defined as

- a) the appearance of sight threatening CNV which was not previously suspected or thought to be present or
- b) evidence of new haemorrhage and/or subretinal fluid (SRF) or
- c) a documented recent visual decline in the presence of CNV or
- d) an increase in the CNV lesion size between visits

5. It is advised that the ranibizumab summary product characteristics (SmPC), and the NICE

Guidance on anti-VEGF therapies in AMD should be followed wherever possible.

Ranibizumab treatment is initiated with a loading phase of three injections at intervals of 4 weeks followed by a maintenance phase in which patients are monitored with ETDRS (LogMAR) BCVA, history and examination, and OCT and/or angiographic examination. The interval between two doses should not be shorter than 4 weeks.

It is expected that all patients will receive the 3 loading doses of ranibizumab, unless there are particular contraindications.

6. Other considerations when commencing treatment

a) Bilateral active CNV lesions

It is reasonable to treat both eyes in any one individual simultaneously, in the presence of bilateral active subfoveal CNV, as long as asepsis is observed. For such simultaneous bilateral intravitreal injections, a separate set of instruments must be used for each eye. Similarly, separate vials of ranibizumab should be used for each eye. The patient should be made aware of the usual cumulative risks of sequential injections either to each eye on separate visits or to both eyes on the same visit.

b) Predominantly haemorrhagic lesions

Foveal haemorrhage or haemorrhage of greater than 50% of the total CNV lesion, are not considered reasons to withhold treatment.

c) Raised intraocular pressure

Elevated intraocular pressure (IOP), even of >30mm Hg, should not preclude treatment provided the IOP is treated simultaneously.

d) Intraocular surgery

It is advised that in the presence of wet AMD and cataracts, the wet AMD should be treated and CNV activity controlled before proceeding to cataract surgery, wherever possible. If CNV is diagnosed after intraocular surgery or there is reactivation, it is not necessary to allow 28 days recovery before commencing ranibizumab. Attention, however, needs to be paid to the cataract wound.

7. Criteria for not commencing treatment

It is recommended that treatment with ranibizumab should not be commenced in the presence of:

- a) Permanent structural damage in the fovea.
- b) Evidence or suspicion of hypersensitivity to ranibizumab, or similar product. Such evidence should lead to avoidance of therapy, and alternate treatments sought.

B. Criteria for Continuation of treatment

It is recommended that after the three loading doses, ranibizumab should be continued at 4 weekly intervals if:

- a) There is persistent evidence of lesion activity
- b) The lesion continues to respond to repeated treatment
- c) There are no contra-indications (see below) to continuing treatment.

Disease activity is denoted by retinal, subretinal, or sub-RPE fluid or haemorrhage, as determined clinically and/or on OCT, lesion growth on FFA (morphological), and/or deterioration of vision (functional).

C. Criteria for temporarily discontinuing treatment (dose withholding)

Consider temporarily discontinuing treatment if:

1. There is no disease activity

The disease should be considered to have become inactive when there is:

- a) Persistent fluid in the absence of FFA leakage or other evidence of disease activity in the form of increasing lesion size, or new haemorrhage or exudates (i.e. no increase in lesion size, new haemorrhage or exudates)
- b) No re-appearance or further worsening of OCT indicators of CNV disease activity on subsequent follow up following recent discontinuation of treatment.
- c) No additional lesion growth or other new signs of disease activity on subsequent follow up following recent discontinuation of treatment.
- d) No deterioration in vision that can be attributed to CNV activity.

2. **There has been one or more adverse events related to drug or injection procedure including:**

- a) endophthalmitis
- b) retinal detachment
- c) severe uncontrolled uveitis
- d) ongoing periocular infections
- e) other serious ocular complications attributable to ranibizumab (drug) or injection procedure
- f) thrombo-embolic phenomena, including MI or CVA in the preceding 3 months, or recurrent thrombo-embolic phenomena which are thought to be related to treatment with ranibizumab
- g) other serious adverse events (SAE) e.g. hospitalisation.

D. Criteria for Permanent discontinuation of treatment

Consider discontinuing treatment permanently if there is:

- 1. a hypersensitivity reaction to ranibizumab is established or suspected
- 2. Reduction of BCVA in the treated eye to less than 15 letters (absolute) on 2 consecutive visits in the treated eye, attributable to AMD in the absence of other pathology
- 3. Reduction in BCVA of 30 letters or more compared to either baseline and/or best

recorded level since baseline as this may indicate either poor treatment effect or adverse event or both

- 4. There is evidence of deterioration of the lesion morphology despite optimum treatment. Such evidence includes progressive increase in lesion size confirmed with FFA, worsening of OCT indicators of CNV disease activity or other evidence of disease activity in the form of significant new haemorrhage or exudates despite optimum therapy over 3 consecutive visits.

E. Criteria for discontinuing treatment and discharging patient from hospital eye clinic follow up

Consider discharging the patient from long term hospital follow up if:

- 1. Decision to discontinue ranibizumab permanently has been made
- 2. There is no evidence of other ocular pathology requiring investigation or treatment
- 3. There is low risk of further worsening or reactivation of wet AMD that could benefit from restarting treatment e.g. very poor central vision and a large, non-progressive, macular scar.