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Cover image Undine and drop bottles
Courtesy of Mr Richard Keeler, Curator Museum of the Royal College of Ophthalmologists. See p 26

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Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials

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ABSTRACT

Background: Neovascular age-related macular degeneration (AMD) has a poor prognosis if left untreated, frequently resulting in legal blindness. Ranibizumab is approved for treating neovascular AMD. However, further guidance is needed to assist ophthalmologists in clinical practice to optimise treatment outcomes.

Methods: An international retina expert panel assessed evidence available from prospective, multicentre studies evaluating different ranibizumab treatment schedules (ANCHOR, MARINA, PIER, SAILOR, SUSTAIN and EXCITE) and a literature search to generate evidence-based and consensus recommendations for treatment indication and assessment, retreatment and monitoring.

Results: Ranibizumab is indicated for choroidal neovascular lesions with active disease, the clinical parameters of which are outlined. Treatment initiation with three consecutive monthly injections, followed by continued monthly injections, has provided the best visual-acuity outcomes in pivotal clinical trials. If continued monthly injections are not feasible after initiation, a flexible strategy appears viable, with monthly monitoring of lesion activity recommended. Initiation regimens of fewer than three injections have not been assessed. Continuous careful monitoring with flexible retreatment may help avoid vision loss recurring. Standardised biomarkers need to be determined.

Conclusion: Evidence-based guidelines will help to optimise treatment outcomes with ranibizumab in neovascular AMD.

Neovascular age-related macular degeneration (AMD) causes severe and irreversible vision loss, and frequently results in legal blindness, with resulting considerable economic burden.[1–5]

Pharmacotherapies against vascular endothelial growth factor-A (VEGF-A), a key factor in the pathogenesis of choroidal neovascularisation (CNV), have been introduced to treat neovascular AMD.[6–10] Pegaptanib sodium (Macugen, EyeTech, New York), a selective antagonist of the 165 isoform of VEGF-A,[11] was approved by the Food and Drug Administration (FDA) in December 2004. Ranibizumab (Lucentis, Novartis Pharma AG, Basel, Switzerland and Genentech, South San Francisco, California), a recombinant, humanised, monoclonal antibody Fab fragment that inhibits all biologically active VEGF-A isoforms, was approved by the FDA in June 2006 (monthly 0.5 mg intravitreal injection).[12–14] Bevacizumab (Avastin, Genentech), a full-length monoclonal antibody against all VEGF-A isoforms, was approved by the FDA for colorectal cancer in 2004 and later used intravitreally off-label in neovascular AMD.[15 16] Head-to-head ranibizumab and bevacizumab trials are under way but are not scheduled to report until 2010 (CATT (NCT00593450), VIBERA (NCT00559715), IVAN and GEFAL trials).

Although preliminary guidelines for anti-VEGF therapies exist,[16–22] more comprehensive clinical practice guidelines on applying ranibizumab are needed to optimise patient outcomes. Ranibizumab Phase III clinical trials in neovascular AMD have studied different treatment schedules, doses and populations, and this review applies the trial evidence to ranibizumab use in clinical practice. We evaluated the licensed 0.5 mg of ranibizumab dose, shown to be more effective than 0.3 mg in pivotal trials,[12 13 23] and focused solely on ranibizumab because: pegaptanib showed less visual-acuity (VA) decline than sham injection, although on average treated patients continued to experience vision loss;[11] bevacizumab use in neovascular AMD currently remains off-label with relatively few reported clinical trial data and, to date, no completed large, prospective, randomised clinical trials.[16]

RANKING AND SOURCES OF EVIDENCE

Level I indicates strong evidence (eg, well-designed, randomised, controlled clinical trials that address the issue in question); level II indicates substantial evidence that lacks some qualities (eg, derived from randomised clinical trials but with flaws, such as absent control group or sufficiently long follow-up); level III indicates relatively weak evidence (eg, derived from non-comparative studies without controls, descriptive studies, panel consensus or expert opinion).

A PubMed literature search on 31 October 2008 (restricted to English literature; no date restriction) using the MeSH term macular degeneration (multi) and the words vascular endothelial growth factor, ranibizumab or Lucentis yielded 187 papers. The Cochrane Register of Controlled Trials and the Cochrane Database of Systematic Reviews were also searched, yielding 16 and four references, respectively. A total of 129 relevant articles were selected, from which 74 were selected for detailed assessment. Additional data from abstracts considered relevant to this manuscript were included in the analysis. From this detailed literature search, the primary sources of data were all level I evidence: the Phase III trials MARINA[13] and ANCHOR,[12 24] including quality-of-life and subgroup analyses,[25–28] and the Phase IIIb trials PIER,[23] SAILOR Cohort 1,[29] SUSTAIN (assigned level II evidence as only interim data currently available),[30] and EXCITE[31]. A small, open-label study

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Table 1 Recommendations for treatment indication with ranibizumab

Parameters for recommended indication	Evidence	Level of evidence
Predominantly classic, minimally classic and occult (with no classic component) CNV*	All CNV types included in PIER, EXCITE, SUSTAIN, SAILOR and PrONTO; predominantly classic CNV in ANCHOR and minimally classic and occult (with no classic component) CNV in MARINA	Level I evidence (MARINA, ANCHOR, PIER, EXCITE and SAILOR), supported by level II (SUSTAIN) and III evidence (PrONTO)
Subfoveal (including juxtafoveal) lesions	Subfoveal CNV (defined as including the foveal centre within the boundaries of the CNV) was an inclusion criteria in all studies	Level I evidence (MARINA, ANCHOR, PIER, EXCITE and SAILOR), supported by level II (SUSTAIN) and III evidence (PrONTO)
Active disease	Active disease was an inclusion criteria in the MARINA and PIER studies†	Level I evidence (MARINA and PIER) and level III evidence
Abnormal retinal thickness with evidence of intraretinal or subretinal fluid by OCT		
Intraretinal or subretinal haemorrhage		
Enlargement of CNV size on FA unless solely due to dry, fibrotic staining		
New/persistent leakage on FA		
Any baseline VA	Baseline VA 20/40 to 20/320 was an inclusion criterion in all studies‡	Level I evidence (MARINA, ANCHOR, PIER and SAILOR), supported by level II evidence (SUSTAIN)
Efficacy was seen over the whole VA range studied in trials, so it is expected that benefit would occur independently of VA whenever progressive vision loss is expected due to an active lesion	Baseline VA better than 20/40 or worse than 20/320: no clinical data available, expert opinion based on extrapolation of clinical evidence	Level III evidence
Serous PED, RAP or PCV can be considered for ranibizumab treatment but might not respond as well as expected from average trial outcomes	No detailed clinical trial evidence currently available	Level III evidence

*In the MARINA and PIER studies, evidence of recent disease progression was required for eyes with minimally classic or occult (with no classic) CNV.
†Active disease was defined as meeting any of the following criteria: (1) ⩾10% increase in lesion size by comparing a fluorescein angiogram performed within 1 month preceding day 0, inclusive, compared with a fluorescein angiogram performed within 6 months preceding day 0, inclusive; (2) resulting in VA loss of >1 Snellen line (or equivalent) and occurring at any time within the prior 6 months; (3) subretinal haemorrhage associated with CNV within 1 month preceding day 0; or (4) (not included in MARINA criteria) classic CNV comprised ⩾50% of the CNV lesion area.
‡Snellen equivalent assessed by Early Treatment Diabetic Retinopathy Study charts; the PrONTO study included patients with baseline VA from 20/40 to 20/400.
CNV, choroidal neovascularisation; FA, fluorescein angiography; OCT, optical coherence tomography; PCV, polypoidal choroidal vasculopathy; PED, pigment epithelial detachment; RAP, retinal angiomatous proliferation; VA, visual acuity.

(PrONTO; level III evidence) also provided relevant information,[32] and appropriate abstracts covering recent Phase III trial findings (unpublished) were included.

NATURAL HISTORY AND ASSESSMENT OF NEOVASCULAR AMD

What is the natural history or prognosis of untreated neovascular AMD?

A systematic review covering the period 1980 to 2005 assessed studies reporting disease progression outcomes for untreated patients with neovascular age-related macular degeneration (AMD), by using random effects meta-analyses.[4] Of 53 studies included, there were 28 randomised clinical trials (RCTs), totalling 4362 patients with untreated neovascular AMD. The most recent RCTs of antivascular endothelial growth factor therapy (VISION,[11] MARINA[13] and PIER[23]) were not included. The systematic review found that, on average, one logarithm of the maximum angle of resolution (logMAR) line of visual acuity (VA) was lost by 3 months, three lines by 1 year and four lines by 2 years. This prognosis is relatively similar to that in MARINA, in which sham-treated eyes lost an average of two lines by 1 year and three lines by 2 years and in PIER, in which sham-treated eyes lost an average of three lines by 1 year. In this review, a doubling of the visual angle was found in the first year. At baseline, 20% of eyes already had a VA <20/200, but this proportion rose to 76% by 3 years.[4]

How should neovascular AMD be diagnosed?

Accurate diagnosis and classification of neovascular AMD using recommended criteria is critical. Assessment should include: history (duration and characteristics of visual symptoms); VA; stereoscopic biomicroscopic slit-lamp fundus examination (78 D or similar lens); fluorescein angiography (FA); and, where possible, optical coherence tomography (OCT).

Logarithm of the minimum angle of resolution (logMAR) VA is preferable to Snellen VA due to its greater sensitivity, ordered progression of letter size (five equally readable letters per line), reproducibility and ability to compare with published trial data.[33] The Snellen chart has several limitations such as visual crowding and variable legibility of the letters. Non-geometric letter size progression and a variable number of letters per line also prevent Snellen outcomes from being easily equated to letters or lines of VA change.[34 35]

For initial diagnosis, FA is deemed mandatory to detect CNV, exclude non-AMD causes (eg, neovascularisation due to myopia, pseudo-xanthoma elasticum, birdshot choroidopathy, etc, which could respond differently to AMD neovascularisation) and determine CNV extent, type, size, location, degree of leakage and proportion of various lesion components.[18 36] OCT is also strongly recommended initially to define the extent of retinal thickening and both the localisation and qualitative pattern of extracellular fluid accumulation.[37 38] Indocyanine Green (ICG) angiography may also be useful in selected cases, eg, when polypoidal choroidal vasculopathy (PCV)[4 39 40] or retinal angiomatous proliferation (RAP)[41–43] is suspected, or the extent of CNV in occult lesions is unclear.

RANIBIZUMAB THERAPY FOR NEOVASCULAR AMD: INDICATIONS AND CONTRAINDICATIONS

Which neovascular AMD lesions should be considered for ranibizumab treatment?

All three major CNV subtypes (predominantly classic, occult (with no classic component) and minimally classic) respond to ranibizumab[12 13] (table 1). Ranibizumab is primarily indicated

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