Brolucizumab for wet age-related macular degeneration

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Brolucizumab (Beovu) is a new monoclonal antibody fragment targeting VEGF-A for the treatment of neovascular (wet) age-related macular degeneration (AMD). This article outlines its mechanism of action, place in therapy, clinical efficacy and adverse effects.

The 2018 NICE guideline on the management of age-related macular degeneration (AMD) recommends treatment with an intravitreal anti-vascular endothelial growth factor (anti-VEGF) agent (the monoclonal antibody fragment ranibizumab or the recombinant fusion protein aflibercept) for late AMD (wet active) in patients with vision within a specified visual acuity range and meeting other ophthalmological criteria. These inhibitors bind to VEGF-A and reduce neovascularisation and other changes such as retinal oedema.

NICE could not evaluate the less expensive anti-VEGF monoclonal antibody bevacizumab because it was not licensed for this indication, although a footnote in the guidance indicated that the three anti-VEGF agents aflibercept, bevacizumab and ranibizumab show equivalent clinical effectiveness and safety. NHS Trusts have long offered treatment with products specially prepared from the Avastin formulation of bevacizumab, which is licensed for the treatment of certain cancers. The Medicines and Healthcare products Regulatory Agency (MHRA) recently ruled that prescribing bevacizumab for AMD is a legitimate off-label use and the Court of Appeal has ruled that this use is lawful. A cost effectiveness analysis concluded that the three anti-VEGF options (bevacizumab, ranibizumab and aflibercept) show similar effectiveness, and that bevacizumab is the most cost effective for AMD.

Anti-VEGF treatment is suspended when regular monitoring shows the patient is not benefiting from continued treatment. Switching between anti-VEGF agents can offer a more convenient dose regimen but the clinical benefit may be limited. NICE is now evaluating a new anti-VEGF agent, brolucizumab (Beovu), a monoclonal antibody fragment that binds to VEGF-A. Brolucizumab works by preventing VEGF-A binding to its receptors VEGFR-1 and VEGFR-2, thus suppressing endothelial cell proliferation and decreasing neovascularisation and vascular permeability. Brolucizumab has recently been accepted by the Scottish Medicines Consortium for use within NHS Scotland.

**Indications and dosage**

Brolucizumab is licensed for the treatment of neovascular (wet) AMD in adults.
The recommended dose is 6mg administered by intravitreal injection every four weeks for the first three doses. AMD activity should be assessed at 16 weeks after the start of treatment. Treatment every eight weeks should be considered if AMD is active, or every 12 weeks in patients without disease activity. As has been the case with other anti-VEGF treatments, clinicians may tailor the treatment regimen to individual need. Treatment should be discontinued if the patient is not benefiting from treatment.

Following administration, brolucizumab is absorbed systemically before undergoing proteolysis and renal elimination. No dose adjustment is recommended for older people or in individuals with renal or hepatic impairment, although it has not been studied in people with hepatic impairment or severe renal impairment.

**Efficacy**

Evidence for the efficacy and safety of brolucizumab comes from two randomised phase 3 trials of similar design, HAWK (n=1082) and HARRIER (n=743). Eligible patients were aged ≥50 years (mean age 77 years) and had untreated, active choroidal neovascularisation lesions secondary to AMD affecting the central subfield (the circular area within 1mm around the foveal centre) and comprising >50% of the total lesion area; they also met other ophthalmological criteria. The mean baseline best-corrected visual acuity (BCVA, Early Treatment Diabetic Retinopathy Study letter score) at baseline was approximately 61 letters overall.

Patients were randomised to treatment with brolucizumab 3mg (in HAWK only, subsequently unlicensed dose not discussed further) or 6mg every 12 weeks after the first three loading doses, adjusted to every eight weeks if disease activity was present, or aflibercept 2mg every eight weeks. The primary endpoint was change in mean BCVA from baseline to Week 48 (non-inferiority). Secondary endpoints of AMD activity were analysed for superiority, if non-inferiority (within a margin of four letters difference) was shown for the primary endpoint but there was no superiority test for the primary endpoint.

Approximately 90–93% of patients completed the trial. Over half of all patients treated with brolucizumab remained on a 12-week dose schedule throughout the trial; this proportion increased to around 80–85% in the subgroup with no disease activity in the first 12 weeks.

After 48 weeks, the mean change in BCVA with brolucizumab 6mg was +6.6 letters vs +6.8 with aflibercept in HAWK and +6.9 vs +7.6 respectively in HARRIER (see Figure 1). Brolucizumab was therefore non-inferior to aflibercept (p<0.001). Other analysis showed similar outcomes for the last 12 weeks of the trial (which accommodated differences in dose regimens) and during follow-up to 96 weeks. The proportion of patients with improved visual acuity (≥15 letters gain) at 48 weeks was 33.6% with brolucizumab vs 25.4% with aflibercept in HAWK, and 29.3% vs 29.9% respectively in HARRIER. Loss of visual acuity (≥15 letters) occurred in 4–6% of patients, with no significant difference between the treatments.

Superiority analyses showed a significantly greater effect for brolucizumab over aflibercept for reduction in central subfield thickness, intraretinal and subretinal fluid control, and duration of effect (presence of disease activity at 16 weeks).
Adverse events
The nature and frequency of adverse events were similar for brolucizumab and aflibercept, with ocular events reported by 49.7% vs 47.2% of patients with brolucizumab vs aflibercept in HAWK and 33.0% vs 32.2% in HARRIER. The most common ocular adverse events with brolucizumab were conjunctival haemorrhage, reduced visual acuity, vitreous floaters and eye pain. The incidence of serious ocular events was 3.1% vs 0.8% with brolucizumab vs aflibercept in HAWK and 2.4% vs 1.1% in HARRIER.

Non-ocular events occurred in 64.4% vs 71.7% with brolucizumab vs aflibercept in HAWK and 59.2% vs 57.2% in HARRIER. Non-ocular serious adverse events occurred in 13.1% vs 18.9% respectively in HAWK and 9.5% vs 11.7% in HARRIER.

References
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Declaration of interests
None to declare.

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