London Medicines Evaluation Network Review

Evidence for initiating intravitreal bevacizumab for the management of wet age-related macular degeneration (wet-AMD) in eyes with vision better than 6/12

November 2015

Introduction

NICE approve the use of intravitreal ranibizumab and aflibercept as options for the treatment of wet AMD within their marketing authorisation. However they only recommend treatment in eyes presenting with Best-Corrected Visual Acuity (BCVA) between 6/12 and 6/96, which is consistent with the entry criteria of the pivotal studies. (1-3)

It has been previously shown that if therapy is initiated at good baseline visual acuity (VA), the treated eye is more likely to maintain good vision. The recent study, UK AMD EMR USERS GROUP REPORT V, evaluated ranibizumab and compared the visual outcome of neovascular AMD patients receiving treatment in eyes with vision better than 6/12 versus eyes with vision 6/12 or worse. Real-world data was collected retrospectively over 5 years from multiple centres using electronic medical records and included 12 951 treatment-naive eyes of 11 135 patients. The study found that use of ranibizumab in the earlier treatment group, with baseline VA better than 6/12, was associated with better visual outcomes and longer maintenance of good VA compared with the delayed treatment group (VA 6/12 to >6/24). This was demonstrated without a significant increase in the number of clinic visits or injections. The difference in mean VA outcomes for eyes with baseline vision better than 6/12 vs. 6/12 to >6/24 was significant for 3 years in the second eyes (globally adjusted p values for year 1, 2, 3 were <0.001, 0.001 and 0.01, respectively). But when sub-grouped into first eyes, significant differences were seen for the first 2 years only (globally adjusted p values for year 1, 2, 3 were <0.001, <0.001, 0.40, respectively). Despite similar initial VA at the time of initiation of therapy, the first eyes did worse than the second eyes at 3 years. It is thought that as the second eyes are treated at an earlier disease state, that this may account for the better outcomes at 3 years, even if VA measurement cannot detect the difference. (2)

Ranibizumab and aflibercept are the NICE-approved treatment options for wet-AMD, however intravitreal bevacizumab has also been used outside of its marketing authorisation as an off-label treatment for wet-AMD. As with the licensed treatment options most studies evaluating the use of intravitreal bevacizumab for wet-AMD include eyes with VA of 6/12 or worse (EI-Mollaey). The aim of this review is to summarise the available evidence for initiating intravitreal bevacizumab for wet-AMD in eyes with vision better than 6/12 (20/40 as Snellen equivalent).

Summary of evidence

A systematic search of the literature identified one prospective and three retrospective studies which specifically evaluated the use of intravitreal bevacizumab for wet-AMD in eyes with vision better than 6/12. The prospective study included 90 treatment-naive eyes with neovascular AMD, and aimed to establish the effects of intravitreal bevacizumab in eyes with baseline VA better than 20/40 Snellen equivalent. At 12 months, eyes with good baseline VA (>20/40) had minimal improvement in BCVA (+0.4 letters) but achieved or maintained superior functional outcomes compared with eyes with lower baseline visual acuity (20/40 to 20/100) (78.4 letters vs. 65 letters on average). It is suggested that the minimal improvement in the eyes with better vision than 20/40 may be the result of a ceiling effect, as the gain in number of letters could be hindered by the limited number of letters needed to obtain a BCVA of 20/20. (4)

The largest retrospective study included 150 treatment-naive eyes with neovascular AMD and good BCVA between 20/20 to 20/40. At a mean follow-up of 20.2 months, treatment with intravitreal bevacizumab stabilised or improved VA in 70.7% of eyes, and 7.3% of eyes lost ≥ 3 Snellen lines. A smaller group of eleven patients (7.3%) who had no loss of vision at baseline (BCVA 20/20), did not achieve any gain or improvement in VA as would be expected; 3 patients remained stable, one patient lost 3 Snellen lines and the remaining seven lost 1-2 lines. The mean final logMAR BCVA for this small cohort of patients was 0.09 ± 0.1 compared to 0.22 ± 0.2 for the full cohort. (5)

Findings of the prospective and large retrospective study were mirrored in two small retrospective case series of eyes with good VA. The first case series (n=96 eyes) demonstrated that in patients with bilateral exudative AMD, the eye with worse vision at baseline had a better prognosis for a gain in VA (+0.07) than the contralateral eyes with the higher VA (+0.05). (6) The smallest case series (n=15 eyes), reported bevacizumab stabilised CNV lesions and maintained VA in 80% of eyes with exudative AMD. No significant difference was found in BCVA at baseline (mean BCVA, 0.89 ± 0.21), and
As previously mentioned, the entry criteria of pivotal wet-AMD studies largely include eyes with baseline VA worse than 6/12 (20/40 as Snellen equivalent). In the Comparison of Age-related Macular Degeneration Treatments Trial (CATT) study, however, 37-39% of patients presented with a baseline VA of ≥20/40 (5). The majority of CATT participants maintained or improved visual acuity relative to their baseline VA following bevacizumab or ranibizumab treatment, although unfortunately the authors did not provide a subgroup analysis of patients who presented with VA of ≥20/40. A subsequent cohort analysis however sought to determine baseline predictors of VA outcomes at 1 year. It was established that eyes with worse baseline VA had lower mean VA scores at 1 year, however, the mean increase in VA was greatest for the group of eyes with baseline VA 20/100 to 20/160, and lowest for the eyes with VA 20/40 or better. Although eyes with worse baseline visual acuity had greater improvement by 1 year, the average improvement was not sufficient to restore VA at 1 year to the same level for all participants. For example, while eyes with baseline VA of 20/100 to 20/160 improved on average 12 letters, their average VA at 1 year was only 20/63, whereas eyes with baseline VA of 20/25 to 20/40 improved on average only 3 letters but achieved an average VA of 20/32 at 1 year. (8)

Overall, the evidence base demonstrates that patients with wet-AMD presenting with good VA (6/12 or 20/40 as Snellen equivalent) show stabilisation of VA after treatment with intravitreal bevacizumab in a clinical setting. A ceiling effect of improvement in eyes with better vision than 20/40 is expected and identification of predictors such as baseline VA allow ophthalmologists and patients to adjust their visual acuity expectations following treatment. Eyes with a low baseline VA have a better prognosis for an improvement in vision than patients starting at a relatively high level. (9) However, maintaining a visual acuity better than 20/40 allows a better quality of life, and therefore early detection and initiating treatment while visual acuity is good is critical. (4,10)

Other RCT studies identified have also included similar patients with VA better than 6/12 but as results were not analysed according to this cohort of patients there is limited data to add to this review. (11,12) Further limitation of this review are that other relevant published studies including a mixture of patients with good and poor VA may not have been identified; full texts of all bevacizumab studies were not hand searched to establish whether a sub-analysis of those eyes with VA better than 6/12 were conducted.

Points for consideration in relation to the literature:

- The majority of the published data identified were descriptive in nature, and consisted mainly of retrospective studies with limited sample sizes and varying (usually short) follow-up periods.
- Overall, the evidence base suggests positive visual outcomes for patients presenting with good VA (≥20/40). It has been suggested that benefit of treatment is difficult to determine given the small range of possible improvement in VA but, as discussed above, change in VA alone is not a good indicator of quality of life; ability to achieve longer term maintenance of good VA is critical.
- The optimal treatment regimen for eyes with good visual acuity has not established. All the published reports used intravitreal bevacizumab at a dose of 1.25 or 1.5mg. The ‘as-needed’ or individualised treatment regimen was used in the studies with or without a loading phase of three injections at intervals of 6-8 weeks. It was not always possible to identify the specific intervals between treatment doses during the ‘as-needed’ treatment phase; one study specified a minimum interval of 4 weeks between the two injections.
- There is limited information on long-term efficacy as follow-up periods were generally short (6-12 months); the longest mean follow period was for 20 months.
- Criteria for retreatment were determined according to OCT and clinical findings such as persistent subretinal fluid or persistent haemorrhage, with subsequent drug administration at the discretion of the treating physician.
- From the available data, fewer injections were used compared with those used in the NICE costing model for ranibizumab in wet-AMD. However, from the descriptive data identified, the number of injections used will vary on an individual patient with follow-up period likely to determine the total number of injections required.
- Safety is not discussed in detail in many of the papers, although no serious ocular adverse events were noted in the studies. Early treatment may result in patients receiving treatment for a longer duration. As the effects of early treatment, in relation to side-effects, have not been investigated in randomised controlled trials ongoing monitoring and collection of data is important.
Supportive evidence

A systematic search of the literature identified one prospective and three retrospective studies, which evaluated the use of intravitreal bevacizumab for wet-AMD in eyes with good baseline visual acuity (VA). The prospective study included 90 patients (90 eyes) with treatment-naive neovascular AMD and aimed to establish the effects of intravitreal bevacizumab in eyes with baseline VA better than 20/40 Snellen equivalent (70 letters). The eyes were treated with intravitreal bevacizumab injections every 6 weeks based on a standard OCT-guided, as-needed re-treatment protocol which did not include a compulsory loading phase. Eligible eyes were enrolled equally into 1 of the 3 groups based on BCVA: Group 1: vision better than 20/40 (n=30); Group 2: vision 20/40 to 20/60 (n=30); and Group 3: vision 20/63 to 20/100 (n=30). If both eyes of the same patient were eligible to enter the study, then the eye with the worse VA was enrolled.

The primary outcome was BCVA at 12 months for each of the 3 groups. Follow-up was continued every 6 weeks or reduced to every 4 weeks if deemed necessary by the treating physician. The results showed that the eyes with baseline VA better than 20/40 achieved or maintained superior functional outcomes compared with eyes with lower baseline visual acuity. For example, at 12 months 93.3% in Group 1 had BCVA between 20/20 and 20/40, compared with 70.0% in Group 2 and 46.7% in Group 3. Conversely, no eyes in Group 1 ended with BCVA of 20/200 or worse, while 20% in Group 2 and 6.7% in Group 3 had BCVA of 20/200 or worse at 12 months. Group 1 had minimal improvement in BCVA but maintained a significantly better mean BCVA compared with eyes with lower baseline visual acuity. For example, mean baseline BCVA was 78.0 letters for Group 1, 66.2 letters for Group 2, and 56.9 letters for Group 3 (P < 0.001); these significant differences were observed at the 12-month follow-up (P < 0.001) with Group 1 maintaining a mean BCVA of 78.4 letters (+0.4 letters) while Group 2 improved to 70.0 letters (+3.8 letters) and Group 3 to 61.1 letters (+4.2 letters). The minimal improvement in group 1 may be the result of a ceiling effect because the gain in number of letters could be hindered by the limited number of letters needed to obtain a BCVA of 20/20. By 12 months, the average number of injections received per patient was 4.4 for Group 1, 4.6 for Group 2, and 3.2 for Group 3 (P = 0.003). No serious ocular or systemic adverse events were noted. (4)

The largest retrospective study identified neovascular AMD patients with good VA (BCVA 20/20 to 20/40) and who were treatment-naïve (n=150 eyes). Patients received three loading doses of intravitreal bevacizumab every 6 weeks and thereafter on an as-needed basis, according to the OCT and clinical findings. The mean duration of follow-up was 20.2 months (6-58 months). At the last examination, VA was stable or improved in 70.7% of these eyes with good VA, and 7.3% of eyes lost ≥ 3 lines; logMAR BCVA 0.22 ± 0.2 for the full cohort. The mean number of injections for all eyes were 11.3 ± 6.2 (3-34). A further sub-analysis according to initial BCVA was performed. The analysis showed that 42 patients (28%) had an initial BCVA of ≥20/30 and logMAR BCVA improved from 0.11 ± 0.07 (0.0–0.18) to 0.16 ± 0.21 (0.0–1.3). For this group of patients VA was stable or improved in 53% of eyes, and 7% lost ≥ 3 lines at the last examination. The mean follow-up time was 18.6 ± 13.5 months (6–58 months) during which the patient received a mean of 10.8 ± 6.5 injections (3–34). A smaller group of eleven patients (7.3%) had no loss of vision at baseline (BCVA of 20/20) and as expected there was no gain or improvement in VA; 3 patients (27%) remained stable, one patient lost 3 Snellen lines and the remaining seven lost 1-2 lines. The mean final logMAR BCVA was 0.09 ± 0.1 (0.0–0.3). These patients were followed for 20.3 ± 14 months (6–58 months), during which they received a mean number of 11.6 ± 4.3 injections (5–19).

Overall, the retrospective series found that the majority of patients presenting with good VA (≥20/40) showed stabilisation or improvement of VA after treatment with intravitreal bevacizumab in a clinical setting. The ocular complication rate was found to be similar to previous studies, although four eyes acquired either glaucoma or ocular hypertension; systemic complications were rare: one case of amaurosis fugax and one case of herpes zoster ophthalmicus were reported. (5)

A smaller retrospective case series studied the efficacy of intravitreal bevacizumab in 15 eyes with exudative AMD and VA of BCVA 0.6 or greater (range 0.6 to 1.2). Patients were treatment naive and received one dose of intravitreal bevacizumab and thereafter additional injections on an as-needed basis, according to OCT and clinical findings such as persistent subretinal fluid or persistent haemorrhage. Patients were followed up every 4 weeks during the first 3 months and every 4 to 8 weeks thereafter with a minimum interval of 4 weeks between the two injections. The mean duration of follow up was 17.4 ± 4.9 months (12 to 29 months). Thirteen of the 15 eyes were treated with bevacizumab alone, seven received a single injection and the remaining six required repeated injections (mean,1.85 injections). Two of the eyes required additional PDT due to increased subretinal fluid or leakage from the CNV.
The study reports that VA declined by more than 0.3 logMAR in two eyes but CNV lesions stabilised and good VA was maintained in 13 of 15 eyes at 12 months. Two eyes received additional PDT; vision declined in one eye but was maintained in the other. The statistics showed that no significant difference was found in BCVA at baseline (mean BCVA, 0.89 ± 0.21; range 0.6-1.2), when compared to 3 months (unchanged) and the final examination (mean BCVA 0.70, p=0.42). BCVA was reported to be 0.8 or more in 12 of the 15 patients (80%) at baseline and at the end of follow-up, nine patients reported BCVA 0.8 or more. The report concluded intravitreal bevacizumab was effective for maintaining or improving VA in exudative AMD with relatively good VA despite the minimum number (1.85) of injections used. No serious ocular adverse events such as acute severe visual loss, endophthalmitis, or RPE tear occurred and no systemic thromboembolic events were noted. (7)

Another small retrospective case series sought to evaluate whether baseline VA influences visual outcomes in patients receiving intravitreal bevacizumab as treatment for bilateral exudative AMD. The case series study included 48 treatment-naive patients (96 eyes) who consecutively received 3 intravitreal bevacizumab injections in both eyes at intervals of 6-8 weeks and were then followed for 6 months. The eyes of each patient were assigned to a study group: group 1, for the eye with the higher visual acuity at baseline, and study Group 2 for the contralateral eye with the lower visual acuity. The case series demonstrated that in patients with bilateral exudative AMD, the eye with worse vision at baseline had a better prognosis for a gain in VA than the contralateral eyes with the higher VA. For example, the eyes with lower VA (Group 2) achieved a greater increase in BCVA (0.07±0.25 LogMAR) compared to the eyes in Group 1 with better VA (0.05±0.29 LogMAR), with a significant difference in change in BCVA between both groups (P=0.02). Similarly, the percentage of eyes which achieved an increase in BCVA of ≥1 line was higher (although not significantly) in Group 2 than in Group 1 (98% vs. 56%). As this is a short study with only 6 months retrospective follow-up, the results should be interpreted cautiously. (6)

A further retrospective study (n=406 eyes) demonstrated that eyes with exudative AMD eyes and a low baseline BCVA have a better prognosis for an improvement in vision than those starting at a relatively high level of BCVA. After 3 injections of bevacizumab, BCVA significantly improved in eyes with a baseline BCVA of less than 0.2 (-0.10±0.43 LogMAR; n=138) and in eyes with a baseline BCVA ≥0.2 and <0.4 (-0.06±0.24 LogMAR; n=117), but BCVA deteriorated in eyes with a baseline BCVA of ≥0.4 (0.09±0.32 LogMAR; n=151). It was unclear from the data whether any of the patients had better vision than 20/40. However it was observed that patients who can still see relatively well may undergo some deterioration of vision initially, despite treatment with intravitreal bevacizumab, and the authors recommend that patients should be counselled as such. (9) This is contrast to the studies described above however, in which vision was generally maintained in eyes with better VA.

Literature search of Embase, Medline and Pubmed:
- EMTREE terms: [*AGE RELATED MACULAR DEGENERATION/ OR *RETINA MACULA AGE RELATED DEGENERATION/] AND *BEVACIZUMAB/ AND [RANDOMISED CONTROLLED STUDY/ OR RANDOMIZED CONTROLLED TRIAL/ OR SYSTEMATIC REVIEW/]
- EMTREE terms: [AGE RELATED MACULAR DEGENERATION/ OR RETINA MACULA AGE RELATED DEGENERATION/] AND BEVACIZUMAB/ AND EARLY INTERVENTION/
- MeSH terms: bevacizumab.af AND [*CHOROIDAL NEOVASCULARIZATION/ OR *MACULAR DEGENERATION/] AND [*VISUAL ACUITY/ OR *EARLY DIAGNOSIS/]
- MeSH terms: bevacizumab.af AND [*CHOROIDAL NEOVASCULARIZATION/ OR *MACULAR DEGENERATION/] AND (good AND visual AND acuity).af
- Pubmed: ((("macular degeneration"[MeSH Terms]) AND "choroidal neovascularization"[MeSH Terms]) AND ("randomized controlled trial"[Publication Type]) OR "review"[Publication Type])) AND bevacizumab[Supplementary Concept]

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References:


