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Oregon Health Authority

Abbreviated Review:
Vascular endothelial growth factor (VEGF) inhibitors

Month/Year of Review: November 2012 **End of Literature Search:** September 2012
Drugs Included: aflibercept, bevacizumab, pegaptanib, ranibuizumab

Research Questions:

- What is the evidence for effectiveness and safety for VEGF inhibitors to treat of diabetic macular edema?
- Is there evidence to determine if one anti-VEGF is more effective or safer than another agent for age-related macular degeneration (AMD), diabetic macular edema (DME), or retinal vein occlusion (RVO)?

Conclusions:

- There is moderate to high quality evidence that VEGF inhibitors improve visual acuity in patients with neovascular AMD and are recommended as first line treatment.
- There is low quality evidence that bevacizumab is equivalent to ranibizumab in improving visual outcomes over two years in neovascular AMD (difference in mean improvement with bevacizumab compared to ranibizumab was -1.4 letters; 95% CI -3.7 to 0.8) and that bevacizumab is associated with a higher rate of serious, nonspecific systemic adverse events over 2 years (31.7% vs. 39.9%; p=0.004, RR 1.30).
- There is insufficient evidence to make comparative conclusions for the use of pegaptanib in AMD.
- There is low quality evidence that aflibercept is equivalent to ranibizumab in maintaining vision at 1 year in the treatment of AMD.
- There is moderate to high quality evidence that anti-VEGF therapy improves visual acuity in patients with DME relative to laser treatment and sham injection, with similar improvements across agents.
- There is insufficient evidence to determine whether there are clinically meaningful differences in health outcomes between the available agents for the treatment of DME.
- There is insufficient direct comparative evidence (no RCTs and indirect observational data) comparing intravitreal bevacizumab with ranibizumab in patients with DME.
- There is insufficient evidence to support the use of pegaptanib in the use of DME.

- There is moderate quality evidence that anti-VEGF therapy improves visual acuity compared to sham injections in central RVO related macular edema with no direct comparative evidence of any agents.

Recommendations:

- Due to a lack of clinical benefit in both AMD and DME over other anti-VEGF agents, make pegaptanib non-preferred.
- There is not strong evidence of superiority of one anti-VEGF agent over another for the treatment of AMD or DME and low quality evidence demonstrating equivalence of bevacizumab to ranibizumab and aflibercept to ranibizumab in AMD. Compare costs of bevacizumab, ranibizumab, and aflibercept.

Reason for Review: There were previously no anti-VEGF agents approved in the U.S. for treatment of DME. However, on August 10, 2012, the Food and Drug Administration (FDA) approved ranibizumab 0.3 mg per month for treatment of DME based on the RISE and RIDE studies.[1] Currently bevacizumab is reportedly used off-label in clinical practice to improve visual acuity in patients with diabetic macular edema refractory to laser therapy and for age-related macular degeneration (AMD). Aflibercept was FDA approved for the treatment of AMD in November 2011 and while ranibizumab was the only agent approved for the indication of RVO, aflibercept recently gained FDA approval for macular edema following central retinal vein occlusion (CRVO). This review will evaluate the available evidence to compare efficacy and safety of the VEGF-inhibitors in the treatment or DME, AMD, and RVO.

Background: DME is a frequent result of diabetic retinopathy and is the foremost cause of central vision loss and a leading cause of blindness in the diabetic population.[2,3] DME is the swelling of the retina due to leakage of fluid from blood vessels within the macula. Vision impairment is very much related to how well the diabetes is controlled and intensive metabolic control remains a highly effective means of controlling retinopathy. The goal of treatment is to preserve current visual acuity and reduce the progression to visual loss. Previous treatment approaches include laser photocoagulation, intravitreal steroid injections, and vitrectomy. Laser photocoagulation has become the gold standard but has not been successful in improving vision, only preserving it, reducing the risk of visual loss by 50% of patients with focal DME.[4,5] Intravitreal steroids may improve visual outcomes associated with DME based on moderate evidence from a Cochrane review of 7 trials (two with low risk of bias, 1 with medium risk of bias, 2 with high risk of bias, and 2 unable to assess).[5] Evidence suggests that intravitreal triamcinolone results in improved visual acuity compared with no treatment, and it can offer short-term improvements in acuity in eyes refractory to laser treatment.[3] However, the risk of elevated intraocular pressure (IOP) and cataracts are increased with steroid use, and are no longer used in favor.[6]

Change in visual acuity is one of the important outcomes evaluated in trials of patients with vascular eye diseases. It is commonly measured as the best-corrected visual acuity (BCVA). The Eye Disease Prevalence Research Group (EDPRS) developed a series of

charts to standardize visual acuity evaluation which are commonly used as a standard outcome measure in RCTs.[6] Serious adverse events of interest include endophthalmitis, glaucoma, stroke, myocardial infarction, other cardiovascular events, and death.

There are currently four anti-VEGF agents available, although only ranibizumab is approved for treatment of DME and only three are approved for one or more ophthalmologic indications. Approval of ranibizumab for the treatment of DME was based on a review of data from two phase III trials, RIDE and RISE, comparing sham injections to ranibizumab 0.3mg and 0.5mg over 24 months. These studies demonstrated a statistically significant difference between treatment and sham groups in the proportion of subjects who gained 15 letters or more in BCVA from baseline to month 24.[7] Ranibizumab treated patients were also less likely to need laser therapy than sham treated patients. Bevacizumab was originally approved for the treatment of colorectal cancer, but has been used off-label for many vascular diseases of the eye, including AMD and DME.[2] Ranibizumab comes from the same parent molecule as bevacizumab but is a humanized monoclonal antibody fragment that binds active forms of VEGF-A, whereas bevacizumab is a full-length antibody and binds to all types of VEGF. In final guidance from NICE in November 2011, ranibizumab was not recommended for use in patients with DME, although the evidence was found to be acceptable supporting its efficacy in sustained gains in BCVA over 2 years, whereas improvement with laser photocoagulation alone is significantly less marked, and it does not provide distinctive innovation above other treatments.[8]

Current guidelines from the American Diabetes Association (ADA) give a recommendation based on level A evidence for laser photocoagulation to reduce the risk of vision loss in patients with high-risk proliferative diabetic retinopathy (PDR), clinically significant macular edema, and in cases of severe nonproliferative diabetic retinopathy (NPDR).[9] These guidelines state that emerging therapy with anti-VEGF seems to halt progression of DME and may in fact improve vision in some patients but do not give specific recommendations regarding therapy. The American Academy of Ophthalmology (AAO) 2008 guidelines also recommend laser photocoagulations as the standard of care, as well as virectomy for advanced proliferative diabetic retinopathy (PDR) which has been shown to increase vision-related quality of life.[10] These guidelines refer that adjunctive treatments such as intravitreal corticosteroids or anti-VEGF may be considered with laser treatment only when in the presence of clinically significant macular edema (CSME). Guidelines from the American Optometric Association (AOA) on care of patient of diabetes mellitus again recognizes the potential impact of anti-VEGF treatment in clinically significant macular edema but has yet to develop recommendations with any specifics regarding treatment with these agents.[11]

A randomized clinical trial by the Diabetic Retinopathy Clinical Research Network found that ranibizumab therapy with either prompt or deferred focal/grid laser treatment provided better visual acuity outcomes compared with prompt laser alone through two years in patients with DME.[12–14] In addition, the RESTORE study was a 12-month, double blind, randomized trial comparing

ranibizumab 0.5mg monotherapy or combined with laser to laser treatment alone and found that ranibizumab alone and in combination with laser were superior to laser monotherapy in improving BCVA at 12 months ($p<0.0001$).[15] Another prospective RCT confirmed that bevacizumab through two years also improved BCVA compared to laser therapy alone.[16,17] At 12 months, there was a significant difference between the mean ETDRS BCVA in the bevacizumab group (61.3±10.4; range 34–79) and laser arm (50.0±16.6; range 8–76; $p = 0.0006$).[16] This was maintained at 24 months (64.4±13.3; range 34-88 vs. 54.8±12.6; range 33-75 for bevacizumab and laser groups, respectively, $p=0.005$). [16]

AMD is a progressive chronic disease of the central retina and leading cause of vision loss worldwide.[18] Patients are typically over 50 years of age and the goal of treatment is to minimize or reverse loss of vision and to maximize the vision-related quality of life related to AMD. Treatment options for AMD include observation, antioxidant vitamin and mineral supplements, photodynamic therapy (PDT) with verteporfin, intravitreal injection of VEGF inhibitors, and laser photocoagulation surgery.[19] VEGF inhibitors have become the standard of care for neovascular AMD and are recommended first line. They have demonstrated improved visual outcomes compared with other therapies. 2008 guidelines from The American Academy of Ophthalmology (AAO) recommend VEGF inhibitors as first line treatment for AMD with no specific distinctions between ranibizumab, bevacizumab, or pegaptanib. These guidelines were developed before the approval of aflibercept. Two controversies in the treatment of AMD with VEGF inhibitors include the preferred dosing regimen and systemic safety. Trials have evaluated a stricter monthly dosing regimen versus a less frequent, as needed protocol based on clinical and imaging features. Safety is a concern as the drugs enter the systemic circulation after ocular injection and there exists a theoretical higher risk of systemic vascular events. Clinical data on the systemic safety is sparse and available studies are not large enough to address safety concerns.

The National Institute for Health and Clinical Excellence (NICE) recommends ranibizumab as an option for wet AMD if the best-corrected visual acuity is between 6/12 and 6/96, there is no permanent structural damage, the lesion size is less than or equal to 12 disc areas, and there is evidence of recent presumed disease progression.[20] It is also recommended that it only be continued in people who maintain adequate response to therapy. NICE guidance states that pegaptanib is not recommended for the treatment of AMD. Based on four randomized controlled trials (RCTs) of ranibizumab and two of pegaptanib, the committee concluded that ranibizumab is more clinically effective than pegaptanib in improving visual acuity, although both are clinically effective in the treatment of wet AMD. [20]

RVO is the second most common retinal vascular disease after diabetic retinopathy with main risk factors being age over 50 and hypertension. [21,22] There are two types of RVO: branch retinal vein occlusion (BRVO) occurring 2-3 times more often than central retinal vein occlusion (CRVO).[21,22] Ophthalmological treatments focus on the prevention and management of the main sight

threatening complications – ocular neovascularization and macular edema. [21] In the absence of either of these complications, there is no evidence that treatment improves outcomes, and treatment is associated with some adverse effects. Macular edema is the most common cause of visual loss in patients with RVO. Laser photocoagulation, steroids, and intravitreal injections of anti-VEGF have been evaluated as treatments, with laser photocoagulation and VEGF inhibitors as the primary treatment options.

Methods:

A Medline literature search ending September 2012 for new systematic reviews and randomized controlled trials (RCT's) comparing VEGF inhibitors in patients with DME, AMD, and RVO was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Institute for Clinical and Economic Review (ICER), Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class review. Randomized controlled trials (RCTs) will be emphasized only if evidence is lacking or insufficient from those preferred sources. The literature search for RCT's was done from the date of search in high quality systematic reviews to current.

Drugs included in review

Anti-VEGF	FDA approved Indications	Mechanism of Action	Dosing
Pegaptanib (Macugen®)	Age-related macular degeneration	Targets only the VEGF 165 isoform	Intravitreous injection every 6 weeks
Bevacizumab (Avastin®)	Tumor therapy	Binds to all types of VEGF	Intravitreous injection every 4 weeks
Aflibercept (Eylea®)	Neovascular (wet) Age-related macular degeneration and macular edema following retinal vein occlusion	Binds VEGF-A and placental growth factor, another angiogenic factor	Intravitreous injection every 4 weeks x 3 months, then every 8 weeks (AMD) Intravitreous injection every 4 weeks (CRVO)
Ranibizumab (Lucentis®)	Neovascular (Wet) Age-related macular degeneration, macular edema following retinal vein occlusion, and diabetic macular edema	Binds all active forms of VEGF-A	Intravitreous injection every 4 weeks. Although less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible for AMD only.

Systematic Reviews: Diabetic Macular Edema

CADTH

In May 2012, CADTH performed a rapid response report including a systematic review of intravitreal bevacizumab for the treatment of DME to evaluate if bevacizumab provides a therapeutic advantage on visual acuity, morbidity, and/or mortality, in comparison with other standard therapy, including ranibizumab.[3] A literature search up to May 2012 was conducted and ten publications were included in the review; one RCT comparing bevacizumab versus placebo, five with laser photocoagulation, and four with triamcinolone therapy. No trials compared bevacizumab with ranibizumab in patients with DME. Mortality and serious adverse events did not differ versus any comparator, and no trials reported on activities of daily living or quality of life.
Bevacizumab was found to improve vision compared to laser therapy. Three trials with a low risk of bias measured effect on BCVA and showed that more subjects demonstrated improvement in 3 lines or greater in the bevacizumab group compared to those in the laser groups at 6 weeks (15% vs. 5% at 6 weeks, risk ratio (RR) 3.33, 95% CI 0.56 to 19.74, p=0.009), 12-16 weeks (21% vs. 7%, RR 3.73 95% CI 1.51 to 9.25, p=0.005; NNT 6), and at 36-52 weeks (23% vs. 9%, RR 2.57 95% CI 1.21 to 5.44, p=0.01; NNT 8). [3]

There was insufficient evidence comparing bevacizumab to triamcinolone (4 trials). None of the trials reported all-cause mortality, mean visual acuity change, activities of daily living, quality of life, or withdrawals due to adverse events. All of the trials had both inadequate masking and allocation concealment. [3]

There was a consistent lack of evidence for the long term safety profile and sparse reporting of adverse events in the reviewed trials. Therefore, in addition to the reviewed literature, an additional non-systematic safety analysis was performed to include systematic reviews in other ocular conditions, a trial comparing bevacizumab and ranibizumab in age-related macular edema, cohort analyses, and a multicentre case series. [3] These results showed no conclusive evidence of serious safety signals with bevacizumab or important differences with other agents, such as ranibizumab, due to the generally lower quality of harms data for bevacizumab. The single head-to-head randomized trial between bevacizumab and ranibizumab for the treatment of AMD suggested an increased risk of non-specific serious systemic adverse events for bevacizumab-treated patients over two years, however the importance of the difference remains unclear.[3]

Institute for Clinical and Economic Review (ICER)

A technology assessment report was prepared by ICER and systematically included 15 RCTs and 8 observational studies of VEGF-inhibitors for DME.[6] Since there are no head-to-head trials comparing VEGF-inhibitors for DME, the authors conducted a series of pairwise indirect meta-analyses to find the mean difference in BCVA change, and the rate ratio of the likelihood of gaining 10 or

more letters of vision, including only fair or good quality trials of 6-24 months duration. For the outcome of mean difference in BCVA, these results found no statistically significant differences between ranibizumab and bevacizumab (MD -4.32; 95% CI -9.13 to 0.49), ranibizumab and aflibercept (MD 0.34; 95% CI -2.81 to 3.49), or bevacizumab and aflibercept (MD 4.66; 95% CI -0.05 to 9.37). Data for pegaptanib were unable to be used for the analysis in change in BCVA. Indirect analyses also demonstrated no significant difference in the likelihood of gain of >10 letters between any anti-VEGF therapies (ranibizumab vs. bevacizumab RR 0.71; 95% CI 0.34 to 1.46). Conclusions from these indirect comparisons need to be drawn with caution. Relatively few trials have been conducted in DME and there was between-agent trial heterogeneity in patient populations, duration of follow-up, and treatment regimens.

Zechmeister, et al.

A recent systematic review evaluated whether anti-VEGF leads to better clinical outcomes than current treatments in patients with DME including laser photocoagulation, intravitreal application of glucocorticoids, and vitrectomy.[4] Eleven RCTs were included in the review; 6 of bevacizumab, 3 evaluated ranibizumab, and 1 on pegaptanib. The principles of GRADE were used to assess the quality of evidence and the overall quality of the evidence of anti-VEGF therapy is moderate. There were no head-to-head comparative trials between the three products. This review did not find the evidence to strongly support the superiority of one anti-VEGF agent over another, although overall the quality of evidence was higher for ranibizumab efficacy than for bevacizumab. Quality of evidence for safety of any of the anti-VEGF products is very low and ocular events were the most frequently reported. There was insufficient evidence to support the use of pegaptanib in DME. One study was found comparing pegaptanib with sham injections, and the differences in visual acuity were either not clinically relevant or of unknown significance.

Based on one study comparing bevacizumab with sham injections, low quality evidence demonstrated a significant and clinically relevant improvement in mean visual acuity (effect size -0.21 better). Two studies comparing bevacizumab with laser photocoagulation showed greater and clinically relevant gains in mean visual acuity (high quality evidence). One small study did not demonstrate a difference in visual acuity between bevacizumab and intravitreal steroids.

There was moderate quality evidence, based on one single high quality study that compared with sham injections, ranibizumab significantly improved mean visual acuity and the percentage of patients who gained at least 15 letters was significantly higher. There was also moderate quality evidence that ranibizumab significantly improved visual acuity and vision-related quality of life compared to laser photocoagulation, although the difference was not clinically relevant. No evidence was available comparing ranibizumab to intravitreal steroids.

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Goyal, et al.:

A meta-analysis and systematic review was performed to evaluate the effect of bevacizumab in DME.[2] This review was evaluated by the Centre for Reviews and Dissemination (CRD) and met the criteria for inclusion in the Database of Abstracts of Reviews and Effects (DARE). Four randomized controlled trials were included in the review and were assessed for quality using criteria from the Delphi List including randomization, allocation concealment, baseline group similarity, specified eligibility criteria, blinding, and intention to treat analysis. All four trials were rated as moderate to good quality. Trials included comparisons of bevacizumab with bevacizumab plus intravitreal triamcinolone, with macular laser photocoagulation, or with sham control groups.

At 6 weeks, there was a significant reduction in center subfield macular thickness (WMD -48.2µm, 95% CI -86.2 to -10.2; I^2=71.4%; three RCCTs), but no significant differences at 12 or 24 weeks between bevacizumab and photocoagulation. No significant between group differences were found for intravitreal bevacizumab versus intravitreal bevacizumab plus intravitreal triamcinolone acetonide at any time point. At 6 weeks, there was also a significant improvement in best-corrected visual acuity (BCVA) with bevacizumab compared to control (WMD -0.13 log MAR, 95% CI -0.23 to -0.02; I^2=85.1%; three RCCTs) and at 24 weeks (only 2 trials), but no significant difference was seen at 12 weeks. There was no significant gain in outcomes with the combination of bevacizumab and intravitreal steroids compared to bevacizumab alone. This review demonstrated the short-term beneficial effects of bevacizumab compared to standard laser therapy and that there is no significant benefit of adding steroids to bevacizumab, with an added risk of cumulative side effects. There was insufficient evidence to make conclusions regarding its long term efficacy either used alone or in combination with other treatments for DME. This meta-analysis was limited due to the small number of trials eligible for analysis and most of them were conducted in Iran. CRD concluded that the conclusions should be interpreted with caution due to this main limitation.

Systematic Reviews: Age-related Macular Degeneration

CADTH

A systematic drug class review and economic evaluation for the management of neovascular AMD was conducted by CADTH in 2008 and concluded that uncertainty still exists with no direct evidence demonstrating the effect of timing or retreatment on health and that evidence for bevacizumab's effectiveness was less compelling than other anti-VEGF agents. Pegatanib or ranibizumab were recommended as optimal treatment strategies.[23]

Cochrane Collaboration:

A 2008 Cochrane systematic review was conducted to investigate the effects of, and quality of life associated with, anti-VEGF therapies for the treatment of neovascular AMD.[24] The primary outcome was BCVA after at least one year of follow up, as

demonstrated by loss of 15 or more letters. The literature search was through February 2008 and resulted in five trials in ten reports for the analysis. All five trials were of good methodological quality and there were no direct head to head trials comparing ranibizumab to pegaptanib. At the time of this review, all trials evaluating bevacizumab were still ongoing or were uncontrolled and did not meet the criteria for inclusion. [24]

Compared to sham injections, pegaptanib demonstrated fewer patients losing 15 letters or more (RR 0.70; 95% CI 0.6 to 0.84) based on two trials. The calculated number needed to treat (NNT) was 6.67 for 0.3mg, 6.25 for 1 mg, and 14.28 for 3 mg pegaptanib. [24] The final mean visual acuity was also greater in all three dosages compared to sham, with the weighted mean difference (WMD) ranging from 3.64 to 7.2 letters. [24]

The overall RR for ranibizumab versus sham for loss of 15 or more letters of visual acuity was 0.14 (95% CI 0.10 to 0.22). The calculated NNT was 3.13 for 0.3mg ranibizumab and 3.13 for 0.5 mg (3 trials). [24] Patients treated with ranibizumab had greater mean visual acuity at one year compared with those treated with sham. The WMD for the mean change was 16.9 for 0.3 mg and 17.6 for 0.5mg. [24]

The authors concluded that based on trials of good methodological quality, ranibizumab and pegaptanib demonstrate efficacy in terms of proportion with loss of 15 letters of more and ranibizumab resulted in a greater proportion with loss of 15 letters or more than pegaptanib.[24]

Mitchell, et al:

A literature search up to June 2010 was used to review ocular and systemic events in AMD with the treatment of ranibizumab and bevacizumab. Nine prospective, randomized, controlled trials considered Level I evidence (8 for ranibizumab and 1 for bevacizumab) and 11 studies considered to be Level II evidence (five ranibizumab and 6 bevacizumab) were included. Level I evidence was defined as strong evidence and level II indicates substantial evidence that lacks some qualities or study flaws. One comparative study of the two agents was included.[25]

Seven large trials of level I evidence including 1301 demonstrated significant improvements in visual acuity in patients with AMD with the use of ranibizumab versus sham, in combination with PDT versus PDT, and in combination with PDT versus sham-PDT. The range of mean visual acuity change in letters from the studies was -1.6 to +11.3 and comparators from -16.3 to -7.8. Four additional open-label studies with 4484 patients also demonstrated significant improvements versus usual care following, although these studies compared different dosing and treatment schedules of ranibizumab. [25]

Six studies (5 being of level II evidence) of bevacizumab included 424 patients and demonstrated significant improvements in visual acuity, as assessed by mean gain of letters. The one trial of Level I evidence compared bevacizumab 1.25mg to PDT/pegaptanib/sham in 131 patients. There was a significant improvement in mean gain of letters (+7 for bevacizumab versus -9.4, p<0.001). There were low rates of serious ocular adverse events and two myocardial infarctions (3.1%).[25]

One small (n=20) study compared the efficacy of ranibizumab and bevacizumab over 6 months and resulted in bevacizumab with a tendency to be associated with a greater gain of letters from baseline, and ranibizumab with a greater reduction in central macular thickness. Differences between the groups were not statistically significant. One year data demonstrated similar results (+6.3 letters for ranibizumab vs. _12.1 for bevacizumab). [25]

Limited safety results could be concluded from the bevacizumab trials, as only three of the studies reported details of adverse ocular or systemic events. Results of this study demonstrated that Level I and Level II evidence supports the efficacy and safety of ranibizumab in wet AMD and that data suggests bevacizumab may also provide efficacy, with insufficient evidence to determine the safety profile of bevacizumab. [25]

Systematic Reviews: Retinal Vein Occlusion

Cochrane Collaboration

A 2010 Cochrane systematic review was performed to investigate the effectiveness and safety of anti-VEGF therapies for the treatment of macular edema secondary to central retinal vein occlusion (CRVO).[26] A literature search through August 10, 2010 found only two RCTs comparing an anti-VEGF agent to sham injection that met the inclusion criteria; both considered to have a low risk of bias although both with relatively small sample sizes and short follow-up periods (six months and 30 weeks). The primary outcome was defined as the proportion of patients with an improvement from baseline in BCVA of greater than or equal to 15 letters or 3 lines on the ETDRS Chart, which has been the standard primary outcome measure for evaluating the efficacy of treatments for retinal diseases. [26]

One of the included trials (Wroblewski) compared pegaptanib (n=33) with sham injection (n=32) for 30 weeks in patients with CRVO-macular edema. The other study (CRUISE) was a sham-controlled trial of ranibizumab comparing 0.3 mg (n=132) or 0.5 mg (n=130) ranibizumab to sham injection (n=130) for six months. The two trials included patients with similar baseline characteristics and mean age. [26]

In the Wroblewski study, there was no significant difference demonstrated between the groups in the primary endpoint. In the sham group, 28% of patients gained 15 or more letters compared to 36% in the 0.3 pegaptanib group (p=0.48) and 39% in the 1.0 mg group (p=0.35). [26] There was a significant difference in average visual acuity gain at week 30 in the 1.0 mg group compared to sham (+9.9 letters vs. +3.2 letters, p=0.02; 95% CI 1.5 to 24.6 letters). The difference was not statistically significant between 0.3 mg pegaptanib and sham (+7.1 letters vs. +3.2, p=0.09, 95% CI -1.3 to 21.8 letters). [26] No quality of life or visual functioning data were included.

In CRUISE, there was a significant difference in mean change BCVA at 6 months between both ranibizumab 0.3 mg and 0.5 mg compared to sham (+12.7 letters 0.3 mg vs. +14.9 letters 0.5 mg vs. +0.8 letters sham, p<0.00001). At six months, the percentage of patients gaining 15 letters or more from baseline was also significantly higher in both treatment groups compared to sham (P<0.0001). For the 0.3 mg group the RR was 2.73 (95% CI 1.79 to 4.17) and was 2.82 (95% CI 1.85 to 4.29) for the 0.5 mg ranibizumab group compared to sham. [26] There were few serious adverse ocular events at six months and some systemic serious adverse events occurred in all groups (one non-fatal myocardial infarct in each group). [26] There was also an improvement in quality of life as measured by the National Eye Institute Visual Functioning Questionnaire 25 item instrument (NEI VFQ-25) in the treatment groups compared to sham.

The authors of this review concluded that the available RCT data presents relatively good evidence that repeated treatment of non-ischemic CRVO related macular edema with the anti-VEGF agents' ranibizumab or pegaptanib may improve numerous outcomes at six months. However, the applicability of the evidence to clinical practice is relatively limited, and there were no data on bevacizumab or other agents. [26]

The Royal College of Ophthalmologists

Guidance for the management of RVO was updated in 2010 due to developments in treatment options.[27] This was based on a literature search through February 2010 for selected RCT's, systematic reviews, and observational studies. Relevant literature was identified and the level of evidence was graded. Guidelines are separated into recommendations for BRVO and CRVO. For macular edema associated with CRVO, the guidelines give grade A strength of evidence for the use of ranibizumab in macular edema based on results of the CRUISE trial and grade D for the strength of the evidence supporting the use of bevacizumab due to an unknown dosing schedule and unclear long-term outcomes. [27]

In macular edema associated with BRVO, guidance also demonstrated grade A strength of evidence for ranibizumab based on results from the BRAVO study which compared it to sham over six months. [27] The BRAVO study was a 12-month, randomized trial that

included a 6-month, injection-controlled treatment period followed by a 6-month observation period In this study, sixty-one percent of subjects in the ranibizumab 0.5mg group achieved a 15 letter gain vs. 29% in the sham treated group and the mean improvement in BCVA at month 12 in the sham group than that of the 0.3 mg and 0.5 mg treatment groups ($p<0.01$). Bevacizumab was given grade B strength of evidence based on increasing short-term data supporting that multiple injections may reduce macular edema associated with BRVO. [27]

Ranibizumab vs. Bevacizumab (details in evidence table in Appendix 1):

Subramanian et al.

The first head to head trial of bevacizumab and ranibizumab in AMD was a small (n=22), 1-year, prospective, single-center, randomized, double-blind study comparing bevacizumab and ranibizumab for the treatment of neovascular AMD. Patients were randomized 2:1 to bevacizumab or ranibizumab. Patient's received monthly treatment for 3 months followed by an as needed dosing schedule. Twenty-two (78.6%) patients completed the year of follow-up, 15 in the bevacizumab and 7 in the ranibizumab groups. There were no significant differences in mean change in visual acuity (+6.3 letters for ranibizumab and +7.6 etters for bevacizumab, p=0.74) or central macular thickness at one year. The quality of this trial is fair due to the small sample size and inadequate power to detect a real difference. The applicability to the real world population is also limited; as the study population was an almost entirely male, Caucasian patient population in a VA setting.[28]

CATT

Ranibizumab and bevacizumab have been compared in the treatment of age-related macular degeneration (AMD) in the Comparison of AMD Treatment Trials (CATT), a randomized, single-blind, noninferiority trial.[29,30] Patients were randomly assigned and treated with one of four regimens. They received ranibizumab monthly or as needed, or bevacizumab monthly or as needed. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart. One year results demonstrated that bevacizumab and ranibizumab had nearly identical effects on visual acuity (99.2% confidence interval for the difference in the mean change in visual-acuity score within -5 to +5 letters) both when drugs were given monthly and when given as needed. Ranibizumab given as needed was also equivalent to ranibizumab given monthly. The comparison between bevacizumab as needed and bevacizumab monthly and ranibizumab monthly was inconclusive. At 1 year, 24 of the 1185 patients had died and the proportions of patients with arteriothrombotic events were similar among the groups, at 2 to 3% (p=0.97). One or more serious systemic adverse events occurred in 255 patients (21.5%) with no statistically significant differences between the four

groups (p=0.11), but when dosing regimens groups were combined there were 24.1% for bevacizumab and 19% for ranibizumab (p=0.04; RR 1.29 95% CI 1.01 to 1.66), driven primarily by hospitalizations. The rates of death, myocardial infarction, and stroke were numerically higher in the bevacizumab-treated groups, but the differences were not statistically significant when compared to ranibizumab (p>0.2). One major limitation of the fair-poor quality CATT trial is the incomplete blinding to the assigned study groups. If receiving ranibizumab, this was displayed in patients' billing documents which unblinded drug assignments, although the assessors remained blinded. The study size was also not sufficient to evaluate drug safety.

After year 1 of the CATT study, patients initially assigned to monthly treatment were reassigned randomly to either continue receiving monthly treatments or switch to as-needed treatments and year two was conducted to describe longer-term effects and the impact of switching from monthly to as-needed treatment.[30] Patients assigned to as-needed treatment initially had no change in assignment. Most of the change in mean visual acuity occurred during year 1, with relatively little change during year 2. There was no significant difference in visual acuity score between the drugs or between the different regimens. The difference in mean improvement with bevacizumab compared to ranibizumab was -1.4 letters (95% CI -3.7 to 0.8) and the difference between those treated by an as-needed regimen compared to those treated monthly was -2.4 letters (95% CI -4.8 to -0.1). [30] There was no significant difference in the proportion of patients without a decrease in vision of 15 letters or more between the groups (88.4% for bevacizumab vs. 93.3% for ranibizumab, p=0.24). Small differences in mean gain in visual acuity emerged between dosing regimens.[30]

Two year data demonstrated no significant difference in the number of patients who died (5.3% vs. 6.1%; p=0.62), proportion of patients with arteriothrombotic events (4.7% vs. 5.0%; p=0.89), or venous thrombotic events (0.5% vs. 1.7%; p=0.054) between patients assigned to ranibizumab and bevacizumab, respectively. [30] The higher rate of serious adverse events observed in patients in the bevacizumab group persisted during year 2 (31.7% vs. 39.9%; p=0.004, RR 1.30). Patients treated as-needed had higher rates of serious adverse events than patients treated monthly (RR 1.20; 95% CI 0.98-1.47; p=0.08). [30]

<u>IVAN</u>

A UK equivalent of the CATT study (IVAN trial) was conducted to compare the efficacy and safety of ranibizumab and bevacizumab in AMD in a noninferiority trial. Although still ongoing, interim results from a pre-specified 1 year analysis have been published. A total of 610 patients were randomized to 4 groups: ranibizumab or bevacizumab, given either every month or as-needed.[31] Both groups received 3 months of treatment and then were allocated to continuous or as needed treatment. Patients and clinicians were blinded to drug allocation but not to treatment regimen allocation. The primary outcome was best-corrected distance visual acuity measured as ETDRS letters, with a noninferiority limit of 3.5 letters. The difference between drugs (bevacizumab minus

ranibizumab) was -1.99 letters (95% CI -4.04 to 0.06) and between treatment regimens was -0.35 letters (95% CI -2.40 to 1.70), favoring continuous therapy. [31] Overall, the comparison between study drugs was inconclusive using the 3.5 letter limit and as-needed treatment was shown to be equivalent to monthly treatment. There were no significant differences between drugs or regimens for quality of life. There were no differences at year 1 between drugs or treatment regimens in mortality, the odds of a serious adverse event, and arteriothrombotic events occurred infrequently, but more often with ranibizumab than bevacizumab. [31]

Authors of the IVAN study also combined results from the CATT study and by Subramanian to develop a weighted mean difference in visual acuity of 1.06 letters in favor of ranibizumab (95% CI -0.29 to 2.41 letters), meeting the noninferiority margin to establish equivalence of the two drugs. The pooled analysis also showed no difference between the drugs in mortality or arteriothrombotic events (p=0.34 and p=0.55, respectively). [31]

There are no head-to-head trials comparing bevacizumab to ranibizumab in patients with DME. There has been one retrospective study with many limitations, including its design, small population studied (n=29), short duration of only 1 injection, and potential unblinding of the patients. This low quality study demonstrated no significant difference in median change in BCVA between bevacizumab and ranibizumab (4.5 letters vs. 6 letters, p=0.58).[32]

<u>New Drug: Aflibercept (Eylea)</u>

Aflibercept was FDA approved for the treatment of AMD in November 2011.[33] Approval was based on two fair to good quality randomized, double blinded, non-inferiority Phase III trials (VIEW 1 and VIEW 2) in 2,412 patients, comparing monthly and every-2-month dosing of aflibercept with monthly ranibizumab in patients with neovascular AMD. [33,34] Doses of 2mg every 4 weeks, 0.5mg every 4 weeks, and 2mg every 8 weeks were compared to ranibizumab 0.5 mg monthly. The primary end point was noninferiority in the proportion of patients maintaining vision at week 52 (losing <15 letters on the ETDRS chart). Patients were at least 50 years of age with active primary subfoveal choroidal neovascularization lesions secondary to AMD. Treatment failure was defined as a decrease from baseline in the BCVA by 15 or more letters at two consecutive assessments that were 4 weeks apart.[34]

In both studies, all three doses of aflibercept were non-inferior to ranibizumab in regards to the primary endpoint; the proportion of patients who maintained vision at week 52 with a noninferiority margin of 10% and none of the doses were found to be superior. [33] In addition, all treatment groups experienced improvements in the ETDRS letter scores versus baseline with the most rapid improvement during the first three months of treatment.[33] Only the aflibercept 2mg every 4 week group was statistically superior to ranibizumab (gain of +10.9 versus -8.1 letters), and only in VIEW 1. [34] The proportion of patients who gained more than 15 letters was similar in all treatment groups. The most common side effects include conjunctival hemorrhage, eye pain, cataract,

vitreous detachment, vitreous floaters and increased intraocular pressure.[33],[34] The VIEW studies were not powered to see differences in serious intraocular complications and there was no difference in serious systemic adverse events between the groups.

Aflibercept has also been evaluated in the treatment of DME in one fair quality phase II RCT (DA VINCI) comparing four different doses to macular laser photocoagulation in 221 patients for 6 months.[35] This was a double-blind, sham-controlled study. At 6 months, mean BCVA improved by 8.5-11.4 letters in each group vs. 2.5 letters in the laser group ($p<0.009$ for all comparisons). Greater numbers of patients in each aflibercept group gained greater than 10 and greater than 15 letters compared to laser but the differences were not statistically tested. [35] There was an overall attrition rate of close to 20% and the treatment group had a higher prevalence of proliferative diabetic retinopathy and history of cardiac disease. Statistically significant differences in improvements in BCVA continued to be seen up to week 52 with all treatment groups compared to laser ($p<0.001$) and no significant differences were seen between the treatment groups. The proportion of eyes that gained 15 letters or more was also statistically greater than in the laser treatment group in all groups except the group dosed every 8 weeks.[35]

The Phase III COPERNICUS study was a randomized, double-blind study assessing the efficacy and safety of aflibercept in patients with macular edema associated with CRVO randomized 3:2 to receive aflibercept 2 mg or sham injection monthly for 6 months.[36] This is currently an ongoing, 2 year study with six month data reported and published. A total of 189 subjects were evaluated and the primary efficacy end point was the proportion of eyes with a gain of 15 ETDRS letters or more in BCVA from baseline to week 24. In the efficacy analysis, 56.1% of eyes treated with aflibercept gained 15 letters or more from baseline, compared with 12.3% of sham-treated eyes, with a difference of 43.8% (95% CI 33.0%-56.6%; $p<0.0001$). There were similar occurrences of ocular adverse events in each group (68.4% aflibercept vs. 68.9% sham). Five patients in the sham group compared to one patient receiving treatment discontinued study drug because of ocular adverse events. [36]

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Appendix 1: Evidence Table

ef/ Study esign[1]	Drug Regimens[2]	Patient Population	N	Duration	Efficacy Results[3] (CI, p-values)	ARR/ NNT[4]	Safety Results (CI, p-values)	ARI/ NNH[4]	Quality Rating[5]; Comment
bramanian et 28 3, RCT	Ranibizumab (RZ) Bevacizumab (BZ) Both given every month for the first 3 months. Following the third injection, decision to administer further treatment was guided primarily by optical coherence tomography changes	All Caucasian descent, all but one subject were male, mean age for patients in the BZ and RZ group was 78 and 80 respectively Inclusion criteria: age greate than 50, symptomatic CNV, cooperative patient, baseline visual acuities equal to or better than 20/400 Exclusion criteria: previous treatment for AMD within past year, advanced glaucoma, coexisting macular disease, history of malignant or uncontrolled hypertension, history of thromboembolic phenomena.	RZ = 7 BZ = 15	One year	Visual Acuity: Mean change (letters): RZ: +6.3 BZ: +7.6 Difference between the two groups: + 1.3 ±14.9 (95% CI 0.64-15.5) P=0.74 Mean Number of injections: RZ:4 BZ: 8 P=0.001	N/A N/A	Details of events not provided but stated that no major ocular adverse effects reported and no systemic adverse events were found in those who completed 1-year follow-up.		**Quality Rating**: Fair **Internal Validity**: Selection –2:1 randomizati the research pharmacist re for randomization Performance – Patients an physicians blinded Detection- All other investi office personnel masked to treatment assignments, to a sample size to detect a re moderate effect size differ Attrition – 78.6% of randor patients completed one ye follow-up **External Validity** Recruitment –Subjects volu from clinic; costs of medica were covered by VA. Patient Characteristics – lin applicability due to entire V population, Caucasian male Setting – outpatient VA clir Outcomes – Visual Acuity is outcome, limited safety da available.

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ATT[29] , NI, MC, RCT	Ranibizumab monthly (RZ1) Bevacizumab (BZ1) monthly Ranibizumab as needed (RZ2) BZ as needed (BZ2)	Mean age : RZ1: 79.2 BZ1: 80.1 RZ2: 78.4 Bz2: 79.3 Inclusion criteria: age ≥50, visual acuity between 20/25 and 20/320, active disease Exclusion criteria: Previous treatment with AMD therapy, Previous treatment with intravenous bevacizumab, history of surgical intervention for AMD, concurrent use of systemic anti-VEGF agents, Evidence of significant uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders	RZ1=301 BZ1=286 RZ2=298 BZ2=300	One year	<u>Mean change in visual acuity (VA) at 1 year (no. of letters; non-inferiority limit of 5 letters):</u> RZ1: +8.5±0.8 BZ1: +8.0±1.0 RZ2: +6.8±0.9 BZ2: +5.9±1.0 P=0.16 <u>Proportion of patients who did not have a decrease in visual acuity of 15 letters or more from baseline:</u> RZ1: 94.4% BZ1: 94% RZ2: 95.4% BZ2: 91.5% P=0.29	 NA NS	<u>Serious Systemic Events</u> RZ1: 53 (17.6%) BZ1: 64 (22.4%) RZ2: 61 (20.5%) BZ2: 77 (25.7%) P=0.11 BZ (1+2): 24.1% RZ (1+2):19.0% RR 1.29; 95% CI (1.01 to 1.66). P=0.04 <u>Arteriothrombotic event</u>: RZ1: 7 (2.3%) BZ1: 6 (2.1%) RZ2: 6 (2.0%) BZ2: 8 (2.7%) P=0.97	 NS ARI 5.1% NNH 20 NS	**Quality Rating**: Fair-poor **Internal Validity**: <u>Selection</u> –adequate rando Computerized treatment a with eligibility review prece enrollment; significant diff baseline medical history fo (7.6% vs. 4.2% vs. 4%, 8.7% mean age in bevacizumab g (80.1 years vs. 79.2 for rani <u>Performance</u> – Ophthalmo blinded to drug but not dos schedule (identify known ir Patients were initially mask study drug but may find ou identity of the drug from b documents. <u>Detection</u>- VA examiner bli image graders masked to d schedule; <u>Attrition</u> – Low overall attri analysis which can bias tow equivalence. **External Validity** <u>Recruitment</u> –Most patient were identified from the cl practices at the participatir and from referring ophthalmologists in the co <u>Patient Characteristics – Setting</u> –in US, where many ophthalmologists already c bevacizumab <u>Outcomes</u> – no significant

ATT two year sults[30] , NI, MC, RCT	RZ monthly (RZm): RZ switched (RZs): BZ monthly (BZm): BZ switched (BZs): RZ PRN (RZp): BZ PRN (BZp): RZ monthly = RZ1 BZ monthly = BZ1 RZ PRN = RZ2 BZ PRN = BZ2	Inclusion criteria: age ≥50, visual acuity between 20/25 and 20/320, active disease Exclusion criteria: Previous treatment with AMD therapy, Previous treatment with intravenous bevacizumab, history of surgical intervention for AMD, concurrent use of systemic anti-VEGF agents, Evidence of significant uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders	RZm=146 RZs=138 BZm=135 BZs=131 RZp=287 BZp=270	2 years	Patients with same dosing regimen Mean change in visual acuity (VA) at year 2 (no. of letters; non-inferiority limit of 5 letters): RZ1: +8.8 BZ1: +7.8 RZ2: +6.7 BZ2: +5.0 P=0.21; between drug P=0.046; between regimen Proportion of patients who did not have a decrease in visual acuity of 15 letters or more from baseline: RZ1: 93.3% BZ1: 92.2% RZ2: 92.8% BZ2: 88.4% P=0.24 Patients with dosing regimen reassigned Mean change in visual acuity (VA) at year 2 RZ: -1.8 BZ-3.6 P=0.03; regimen		Deaths: RZ: 32 (5.3%) BZ: 36 (6.1%) P=0.62 RR1.15, 95% CI (0.7-1.9) Serious Systemic Events: RZ: 190 (31.7%) BZ: 234 (39.9%) P=0.004 RR 1.3; 95% CI (1.07-1.57)	NS ARI 8.2% NNH 12	**Quality Rating**: Fair-poor **Internal Validity**: Selection –adequate rando Computerized treatment a with eligibility review prece enrollment; Performance – Ophthalmologist blinded tc assignment; patients were informed of drug assignme insurance and billing docur specified ranibizumab but bevacizumab. In exit interv assigned to RZ and 24.8% a BZ responded they knew w they were on. Detection- VA examiner bli image graders masked to d schedule; Attrition – Low overall attri ITT analysis **External Validity** Recruitment –Most patient were identified from the cl practices at the participatir and from referring ophthalmologists in the co Patient Characteristics – Setting – in US, where man ophthalmologists already c bevacizumab Outcomes - no significant c

'AN[31] C, NI, RCT, DB	Ranibizumab monthly (RZ1) Bevacizumab (BZ1) monthly Ranibizumab as needed (RZ2) BZ as needed (BZ2) RZ = total RZ patients (RZ1 + RZ2) BZ = total BZ patients (BZ1 + BZ2)	Mean age 77.7 ±7.4 40% male Inclusions Criteria: patients aged 50+ years, newly referred for the treatment o nAMD in the first or second eye, with BCVA ≥25 letters read on a standard ETDRS chart. Exclusion criteria: long standing CNV (fibrosis >50% of the total lesion), a greatest linear diameter >6000µm, thick blood involving the centre of the fovea, 8 or more dioptres of myopia or other active ocular disease causing concurrent vision loss. Previous treatment	RZ1=157 BZ1=149 RZ2=155 BZ2=145	Two years; Interim one year results here	Best corrected visual acuity, letters RZ (total): 69 BZ (total): 66.1 Difference of -1.99 95% CI(-4.04 to 0.06)* Monthly (BZ+RZ): 66.8 PRN (BZ + RZ) : 68.4 Difference of -0.35 95% CI (-2.4 to 1.7)* * bevacizumab and discontinuous treatment inferior to continuous treatment if the lower limit of the 95% confidence interva is >-3.5 Proportion of patients who did not have a decrease in visual acuity of 15 letters or more from baseline: RZ1: 93.3% BZ1: 92.2% RZ2: 92.8% BZ2: 88.4% P=0.24	N/A NS NS	Deaths: RZ (total): 6 (1.9%) BZ (total): 5 (1.7%) P=0.81; drug Monthly (BZ+RZ): 1.6% PRN (BZ + RZ) : 2% P=0.74; regimen Serious Systemic Events: RZ (total): 30 (9.6%) BZ (total): 37 (12.5%) P=0.25 RR 1.3; 95% CI (1.07-1.57) Arteriothrombotic events: BZ (total): 1(0.7%) RZ (total): 6(2.9%) OR 0.23; 95% CI (0.05 to 1.07); p=0.03 P=0.34; between regimens	NS NS NS ARI 2.2% NNH 45 NS	**Quality Rating**: Fair **Internal Validity**: Selection – Block randomiz allocations generated by cc and concealed using an int based system; patients sim baseline Performance – Participants clinicians blinded, except ophthalmologists who inje drug were unblinded and h other role in trial. Nobody blinded to whether patient allocated to continue or sto treatment at 3 months. Ac of 98.2% Detection- Trial personnel Attrition – overall attrition ITT analysis performed **External Validity** Recruitment – recruited fro teaching and general hospi Patient Characteristics – m slightly younger than other Setting – United Kingdom Outcomes – Small differen between drugs in BCVA fro clinical perspective

tudy design abbreviations: DB = double-blind, RCT = randomized trial, NI = noninferiority, MC = multicentre, SB = single blinded [2]**Drug Regimens:** RZ = ranibizumab, BZ = bevacizumab, PRN = as needed
breviations: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confi
terval, ARI = absolute risk increase [4]**NNT/NNH** are reported only for statistically significant results [5]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)