

Class Update: Vascular Endothelial Growth Factors

Date of Review: March 2017

Date of Last Review: January 2015

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

Evidence for the anti-vascular endothelial growth factor (anti-VEGF) agents was last reviewed by the Oregon Pharmacy and Therapeutics Committee (P&T) in January 2015. Recently two medications (ranibizumab and aflibercept) have received expanded FDA indications for treatment of diabetic retinopathy in patients with diabetic macular edema. Ranibizumab has also been recently approved for choroidal neovascularization secondary to myopia. This review examines new comparative efficacy and safety data of anti-VEGF therapy for ocular conditions. Treatment of cancer with bevacizumab is not discussed.

Research Questions:

1. Is there any new comparative evidence to assess efficacy of anti-VEGF agents in the treatment of age-related macular degeneration (AMD), macular edema following retinal vein occlusion, diabetic macular edema, or diabetic retinopathy in patients with macular edema?
2. Is there any new comparative evidence to assess incidence and severity of short- or long-term harms associated with anti-VEGF agents?
3. Are there subpopulations of adults (specifically based on age, disease severity, or prior treatment experience) for which there are differences among anti-VEGF agents in efficacy or adverse effects?

Conclusions:

- There is high quality evidence based on data from multiple systematic reviews that there is no difference in best corrected visual acuity between ranibizumab and bevacizumab for neovascular AMD.¹⁻⁴
- There is moderate quality evidence based on systematic reviews of 2 randomized controlled trials (RCTs) of no difference in visual acuity between ranibizumab and aflibercept at 1 or 2 years in patients with neovascular AMD.^{3,4}
- There is no difference in efficacy between aflibercept and bevacizumab for treatment of neovascular AMD (low quality evidence based on indirect evidence).⁴ There is no direct comparative evidence for pegaptanib sodium for the treatment of AMD.
- There is no difference between ranibizumab and bevacizumab in visual acuity for the treatment of macular edema due to retinal vein occlusion (moderate quality evidence).⁴ There is no direct comparative evidence for other agents for the treatment of retinal vein occlusion.
- There is moderate quality evidence of no clinical meaningful difference in efficacy (defined as a change of >15 ETDRS letters) between anti-VEGF agents in patients treated for diabetic macular edema.^{4,5}

- Patients with diabetic macular edema and worse visual acuity at baseline (<69 letters on the Early Treatment Diabetic Retinopathy Study scale [ETDRS]) may have improved visual acuity with aflibercept compared to bevacizumab (low quality evidence based on 1 RCT).^{4,6} There is insufficient evidence to evaluate differences in other subpopulations of adults.
- There is low quality evidence of no difference in visual acuity between ranibizumab and bevacizumab for the treatment of myopic choroidal neovascularization.^{4,7} There was insufficient evidence for other treatments.
- There is no difference in serious ocular events (including endophthalmitis, eye pain, macular hole, macular edema, retinal hemorrhage or reduced visual acuity) between ranibizumab, bevacizumab or aflibercept (low quality evidence).^{3,4}
- Evidence regarding comparative risk of thrombotic events and serious adverse effects with anti-VEGF agents is mixed. Several observational studies demonstrated an increased risk of mortality and cardiovascular events including venous thromboembolism (VTE) and stroke with bevacizumab compared to ranibizumab.⁴ However, higher quality observational studies and systematic reviews of RCTs failed to demonstrate any difference in cardiovascular events between bevacizumab and ranibizumab.^{1,3,4,8} Overall, differences in rate of cardiovascular events or mortality between agents is likely small (moderate quality evidence).

Recommendations:

- After evaluate of comparative costs in the executive session, no PDL changes are recommended.
- Recommend PA criteria for non-preferred drugs which will apply to pharmacy and physician administered claims (see **Appendix 4**).

Previous Conclusions:

- There is high quality evidence of no difference between bevacizumab and ranibizumab for the treatment of neovascular age-related macular degeneration (AMD) in gain in visual acuity at one year (RR 0.90; 95% CI 0.73 to 1.11) or loss of visual acuity (RR 1.00; 95% CI 0.98 to 1.02). Two studies have confirmed that there is no difference in efficacy at two years.
- There is moderate quality evidence of no difference serious ocular adverse events between bevacizumab and ranibizumab in the treatment of neovascular AMD.
- For the treatment of neovascular AMD, there was moderate quality evidence of no significant difference in risk of death between bevacizumab and ranibizumab (3.7% vs. 3.4%; RR 1.10; 95% CI 0.78 to 1.57); p=0.59).
- There is moderate to high quality evidence that anti-VEGF therapy improves visual acuity in patients with diabetic macular edema (DME) relative to laser treatment and sham injection, with similar improvements across agents.
- There is conflicting evidence regarding the comparative risk of serious systemic adverse events between bevacizumab and ranibizumab. A recent Cochrane Collaboration systematic review found low quality evidence of no difference in serious systemic adverse events (RR 1.08; 95% CI 0.90 to 1.31; p=0.41); however, when removing unpublished trials there was a significant difference favoring ranibizumab. The current evidence remains imprecise and suggests that if a difference does exist, it is likely to be small. There is evidence of no difference in arterial thrombotic events (RR 1.02; 95% CI 0.65 to 1.60) between ranibizumab and bevacizumab.
- There is insufficient comparative evidence to make conclusions on the relative efficacy and safety of pegaptanib or aflibercept.

Previous Recommendations:

- Overall, there is no difference in efficacy between ranibizumab and bevacizumab with potentially slight differences in systemic adverse events and no differences in mortality. Evaluate comparative costs in executive session to determine appropriate PDL placement. Maintain pegaptanib and aflibercept as non-preferred due to lower strength evidence.

Background:

Anti-vascular endothelial growth factor (anti-VEGF) agents are indicated for the treatment of a variety of retinal conditions characterized by abnormal blood vessel growth. Choroid neovascularization and macular edema can be caused by a variety of ocular conditions and diseases. They are commonly present in age-related macular degeneration (AMD), diabetic retinopathy, retinal vein occlusion, and myopia. Though the mechanism of treatment for all these conditions is similar, the exact etiology and risk factors for choroidal neovascularization vary by disease state.

Ranibizumab and aflibercept are both approved for neovascular AMD, macular edema due to retinal vein occlusion, diabetic macular edema, and diabetic retinopathy associated with macular edema. Ranibizumab is the only agent FDA-approved for treatment of myopic choroidal neovascularization, and pegaptanib octasodium is only FDA-indicated for AMD. Bevacizumab is primarily indicated for treatment of cancer, but it is used off-label for retinal conditions. In these diseases, vascular damage can trigger inflammatory responses, expression of vascular endothelial growth factor (VEGF), and formation of new blood vessels in the choroid layer of the eye located between the retina and sclera.⁹ Accompanying features of choroidal neovascularization include sub-retinal exudation and hemorrhage, lipid deposits, retinal pigment epithelium detachment, and fibrotic scarring which cause progressive vision impairment and blindness.⁹ Use of anti-VEGF agents in these conditions can help inhibit angiogenesis and preserve vision in these populations. In many RCTs, the visual acuity is evaluated using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. A change of 10-15 letters on the ETDRS chart (corresponding to approximately 2-3 lines) is considered clinically significant.⁴ Definitions for mild, moderate, or significant visual impairment can vary, but stable vision is typically defined as a loss of 15 letters or less.¹ Moderate visual changes correspond to 15 letters or more and severe vision loss is typically defined as a loss of greater than 30 letters (or 6 lines on the ETDRS chart).¹

Age-related macular degeneration is defined as a chronic, progressive retinal disease eventually leading to visual impairment. It is most common in adults greater than 50 years of age and affects approximately 2-6% of older adults in the United States.⁹⁻¹² The exact etiology of age-related macular degeneration is unknown, but it is thought to be caused by a combination of genetic and environmental factors.¹² Incidence increases with age and is more common in white patients compared to other ethnic races.¹⁰ Other risk factors include previous cataract surgery, darker iris pigmentation, prolonged sunlight exposure, smoking history, significant family history, and nutritional factors.^{9,12} Severe visual symptoms are often only associated with late disease and onset of neovascular changes. Visual symptoms can manifest as progressive or sudden visual distortion of objects, difficulties with light adaptation, perceived flashes of light, or central vision impairment.^{9,12} Disease may also be classified as wet (referring to the presence of neovascular changes) or dry (characterized by primarily presence of acellular debris). If untreated, approximately 5% of patients with early disease will progress to late-stage disease within 5 years.¹² Guidelines from the American Academy of Ophthalmology recommend anti-VEGF agents as first-line therapy to manage AMD associated with neovascular changes to slow disease progression.¹³

Anti-VEGF agents are also used to treat diabetic macular edema. In patients with uncontrolled diabetes, chronic exposure to elevated glycemic levels can result in damage to the microvasculature of the eye causing macular edema and retinopathy. Retinopathy is often asymptomatic but can cause progressive visual changes and impairment if untreated. Retinopathy may be classified as proliferative or non-proliferative disease, and it can occur in conjunction with or separately from development of macular edema.⁹ Proliferative diabetic retinopathy is more commonly associated with neovascularization and preretinal or

vitreous hemorrhage.⁹ Risk factors for retinopathy include ethnicity (Hispanic, African American, and Asian patients), uncontrolled diabetes, longer disease duration, history of cataract surgery, and comorbid dyslipidemia or hypertension.⁹ Guidelines from the American Diabetes Association and American Academy of Ophthalmology recommend laser photocoagulation as first-line therapy in patients with proliferative diabetic retinopathy.^{14,15} Anti-VEGF agents are recommended in patients with diabetic macular edema.^{14,15} Recently, the indications for both ranibizumab and aflibercept were expanded to include patients with diabetic retinopathy associated with diabetic macular edema. Approval of anti-VEGF agents in patients with retinopathy was based on secondary analyses of trials in patients with diabetic macular edema. The majority of patients included in these trials had moderate to severe nonproliferative diabetic retinopathy.^{16,17} More patients treated with aflibercept and ranibizumab had an improvement greater than or equal to 2 steps on the diabetic retinopathy severity scale (DRSS) compared to patients given laser photocoagulation therapy or sham injections. The DRSS classifies retinopathy into 5 categories based on observable findings upon dilated ophthalmoscopy (i.e. presence of microaneurysms, intraretinal hemorrhages, venous beading, neovascularization or other vascular abnormalities).¹⁸ Categories include no apparent retinopathy, mild non-proliferative diabetic retinopathy, moderate non-proliferative diabetic retinopathy, severe non-proliferative diabetic retinopathy, and proliferative diabetic retinopathy.¹⁸

Macular edema may also occur as a result of retinal vein occlusion. Risk factors for retinal vein occlusion include older age, hypertension, arteriosclerosis and diabetes.¹⁹ Obstruction of retinal veins leads to decreased circulation, retinal vascular leakage, macular edema, and an increase in intraocular pressure.¹⁹ Depending on the severity and location of the occlusion, visual symptoms may resolve without treatment.¹⁹ However, untreated persistent macular edema may cause progressive visual loss.¹⁹ Guidelines from the American Academy of Ophthalmology recommend use of anti-VEGF agents in patients with macular edema due to retinal vein occlusion in order to reduce vision loss and prevent neovascular complications.¹⁹ Other treatment options include intraocular corticosteroids and peripheral panretinal photocoagulation for patients with neovascularization of the iris and retina.¹⁹

Myopia, also known as nearsightedness or shortsightedness, is a common eye condition affecting approximately 2% of the United States population.⁷ Patients with myopia are able to see close objects clearly, have difficulty seeing objects at a distance.⁷ Patients with pathologic myopia have progressive elongation of the eyeball which eventually leads to thinning of the retinal epithelium and choroid.⁷ In approximately 5-10% of patients with pathologic myopia, choroidal neovascularization is also present.⁷ Approximately 90% of patients with myopic choroidal neovascularization will have progressive vision loss and macular atrophy eventually leading to blindness.⁷ Current standard of care for myopic choroidal neovascularization includes verteporfin photodynamic therapy which has demonstrated stabilization of disease for up to 1 year.⁷ However, treatment has shown little benefit beyond 1 year.⁷ Other treatment options include laser photocoagulation and surgery, but the efficacy of these treatments is limited by high rates of disease recurrence.⁷ Anti-VEGF agents have also been used off-label for the treatment of myopic choroidal neovascularization and have shown promising short-term results. In 2016, ranibizumab was the first anti-VEGF agent FDA-approved for the treatment of myopic choroidal neovascularization.²⁰ It was approved on the basis of results from one RCT demonstrating improvement in vision over the course of 1 year.²⁰

In the Oregon fee-for-service Medicaid population, these medications are given as intravitreal injections and are billed as physician administered drugs. They are not currently billed through pharmacy claims and are not restricted by prior authorization. In the past year (October 2015 to September 2016), bevacizumab, the current preferred agent, accounted for 85% of claims. Of the patients using bevacizumab, approximately 33% had a diagnosis of cancer within the previous year. Twelve percent of claims were for aflibercept and 6% were for ranibizumab during this time.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

In 2015, the Canadian Agency for Drugs and Technologies in Health (CADTH) performed a systematic review of the anti-VEGF agents for treatment of ocular conditions.⁴ The review included 30 RCTs evaluating bevacizumab, ranibizumab and aflibercept for neovascular AMD (13 studies), diabetic macular edema (5 studies), retinal vein occlusion (9 studies), or choroidal neovascularization secondary to pathologic myopia (3 studies).⁴ The primary outcome in these trials was improvement in best corrected visual acuity, typically measured by a gain of 15 or more letters on the ETDRS scale.⁴ In neovascular AMD, there was no difference in the number of patients who experienced a gain of greater than 15 ETDRS letters between ranibizumab and bevacizumab (OR 1.13, 95% CI 0.96 to 1.34) or ranibizumab and aflibercept (OR 1.01, 95% CI 0.75 to 1.37).⁴ In addition, there were no differences between ranibizumab and bevacizumab when comparing the mean difference in best corrected visual acuity (OR 0.51, 95% CI -0.82 to 1.83), the proportion of patients who had a loss of greater than 15 ETDRS letters (OR 0.95, 95% CI 0.70 to 1.27), or the number of patients who progressed to legal blindness (OR 0.46, 95% CI 0.07 to 3.26).⁴ Similarly, no difference in these visual outcomes was observed between ranibizumab and aflibercept.⁴ No trials directly compared aflibercept and bevacizumab in AMD, though results from a network meta-analysis indicate that there is no statistically significant difference between anti-VEGF agents.⁴ In patients with retinal vein occlusion, there was no difference between ranibizumab and bevacizumab in vision gain (OR 1.03, 95% CI, 0.55 to 1.94) or mean difference in best corrected visual acuity (standardized mean difference [SMD] 0.00, 95% CI -0.30 to 0.30).⁴ Data were lacking for other comparisons in patients with retinal vein occlusion.⁴ Direct comparative data for patients with choroidal neovascularization secondary to pathologic myopia was limited to 2 small RCTs (n=80) comparing ranibizumab and bevacizumab which observed no difference in best corrected visual acuity (SMD: -0.13, 95% CI -0.57 to 0.31).⁴ No evidence was found for other anti-VEGF agents. In diabetic macular edema, direct evidence was limited to a single comparative study. Vision gain, measured as greater than 15 ETDRS letters at 1 year, was statistically less common with bevacizumab and ranibizumab compared to aflibercept (OR 0.60, 95% CI 0.40 to 0.80 and OR 0.70, 95% CI 0.44 to 0.98, respectively).⁴ Comparisons between bevacizumab and ranibizumab were not statistically significant.⁴ Mean difference from baseline in best corrected visual acuity was a 13.3 letter improvement with aflibercept compared to a mean 11.2 letter improvement with ranibizumab and 9.7 letter improvement with bevacizumab.⁴ These differences were primarily driven by a subgroup of patients in the aflibercept group who had worse visual acuity at baseline (initial letter score <69). These patients exhibited a greater relative improvement in best corrected visual acuity when on aflibercept compared to bevacizumab (6.50 letters, 95% CI 2.90 to 10.10; p<0.001) or ranibizumab (4.70 letters, 95% CI 1.40 to 8.00; p=0.003). However, these differences did not achieve a clinically significant difference of 10 to 15 ETDRS letters. There was no significant difference in vision loss (> 15 ETDRS letters) between agents.⁴ At 2 years, the difference in visual acuity between ranibizumab and aflibercept was no longer statistically significant.⁶

Harms examined in the CADTH report included adverse events (including increases in intraocular pressure), serious adverse events (particularly arterial thromboembolism, bacterial endophthalmitis and retinal detachment), withdrawals due to adverse events, and mortality.⁴ In neovascular AMD, direct comparative data was not available for comparisons of aflibercept and bevacizumab. In addition, safety data in patients with retinal vein occlusion were limited to a few small RCTs in patients taking ranibizumab or bevacizumab. No comparative safety data were available in patients with choroidal neovascularization. Overall, no difference was observed between agents with regard to these adverse effects in patients with neovascular AMD, diabetic macular edema, or retinal vein occlusion.⁴ However, harms were infrequently reported and studies were not powered adequately to determine differences in these rare adverse effects.⁴ These results must be interpreted with caution. Authors do note that because bevacizumab is not marketed for intravitreal injection, improper handling or preparation may result in increased risk of microbial contamination.⁴ To further evaluate safety of bevacizumab compared to other anti-VEGF agents, an additional 24 observational studies were included in the review.⁴ Data included one large cohort study with more than 383,000 injections of bevacizumab or ranibizumab which demonstrated no difference in risk of endophthalmitis (adjusted OR 0.66, 95% CI 0.39 to 1.09; p=0.11).⁴ Evidence regarding the cardiovascular safety of anti-VEGF agents was mixed. Several observational studies demonstrated an increased risk of mortality and cardiovascular events including VTE and stroke with bevacizumab compared to ranibizumab.⁴ However, these studies also had significant confounding factors including lack of reported cardiovascular risk factors, selection biases, and unequal follow-up times which may bias results in favor of ranibizumab.⁴ Higher quality observational studies failed to demonstrate any difference in cardiovascular events between bevacizumab and ranibizumab.⁴ Therefore, the authors concluded that if properly prepared and stored, bevacizumab is not associated with greater risk of adverse effects compared to other anti-VEGF agents.⁴ Overall, bevacizumab was recommended as the preferred first-line therapy because it demonstrated equivalent efficacy and safety to other anti-VEGF agents and was associated with lower costs.⁴ Ranibizumab or aflibercept may be used in patients non-responsive to bevacizumab (defined as no improvement after 3 months or < 15 letters improvement after 6 months of therapy) or in patients at high risk for cardiovascular disease.⁴ High risk for cardiovascular disease was defined as individuals with clinical evidence of atherosclerosis, have undergone coronary or arterial revascularization, or have prior history of myocardial infarction (MI), cerebrovascular accident (CVA), or peripheral arterial disease.⁴

A systematic review by the Cochrane Collaboration examined direct comparative evidence for efficacy and safety of ranibizumab or aflibercept for the treatment of neovascular AMD.³ Evidence was derived from 2 high quality RCTs (n=2457 patients, 2457 eyes).³ Patients included in these trials were on located in the United States, Canada, Europe, Latin America, Asia Pacific and the Middle East.³ After 1 year of treatment, the best-corrected visual acuity (measured using the ETDRS scale) was similar between treatments (MD -0.15 letters, 95% CI -1.47 to 1.17; high quality evidence).³ The number of patients who achieved significant improvements in the ETDRS scale (>15 letters) was 32% for both groups (RR 0.97, 95% CI 0.85 to 1.11; high quality evidence), and there was no difference in the proportion of patients who lost 15 or more letters (RR 0.89, 95% CI 0.61 to 1.30; high quality evidence).³ In addition, there was no difference in quality of life measures at 1 year (MD -0.39, 95% CI -1.71 to 0.93; high quality evidence).³ Similarly, after 2 years, there was no difference between aflibercept and ranibizumab in the mean change in best corrected visual acuity from baseline (7.2 vs. 7.9 ETDRS letters) or the proportion of patients with greater than 15 letter improvement (RR 0.98, 95% CI 0.85 to 1.12; high quality evidence).³ Overall safety of ranibizumab and aflibercept was comparable.³ The rate of serious adverse events was similar in patients treated with aflibercept or ranibizumab at 1 year (RR 0.99, 95% CI 0.79 to 1.25, moderate quality evidence).³ There was no difference between groups in the rate of arterial thrombotic events, vascular death, non-fatal MI and non-fatal stroke.³ Serious ocular events occurred rarely and results failed to achieve statistical differences (RR 0.62, 95% CI 0.36 to 1.07, moderate quality evidence due to imprecision), though events were less common in the aflibercept group.³ There is moderate quality evidence of no difference in risk for specific adverse events between groups at 1 year, including risk of congestive heart failure events (RR 0.77, 95% CI 0.20 to 2.97), retinal hemorrhage (RR 0.65, 95% CI 0.16 to 2.60), and non-ocular hemorrhagic events (RR 2.30, 95% CI 0.42 to 12.70).³ These events were rare, imprecise, and failed to achieve statistical significance, leading to uncertainty in the true estimate of effect.³ In addition, differences in these all events at 2 years failed to achieve statistical significance.³ Another systematic review reported similar outcomes, with no clinical difference in efficacy or safety between ranibizumab and aflibercept.⁸

A systematic review conducted in 2015 compared bevacizumab to ranibizumab for the treatment of neovascular AMD.² Six high quality RCTs were included in the meta-analysis (n=2612 patients).² The majority of patients included in these trials were on average 76 to 79 years of age.² Overall, there was no difference between bevacizumab and ranibizumab in the mean change in best-corrected visual acuity after follow-up of 1 year (MD -0.40, 95% CI -1.48 to 0.69, p=0.47) or 2 years (weighted MD -1.16, 95% CI -2.82 to 0.51, p=0.17).² Serious adverse events were slightly more common with bevacizumab than ranibizumab at 1 year (18.6% vs 14.9%; RR 1.24, 95% CI 1.04 to 1.48; p=0.02; NNH=27) and 2 years (35.6% vs 29.7%; RR 1.20, 95% CI 1.05 to 1.37; p=0.008; NNH=17).² Though there was no difference in individual risk of death, MI, stroke, or VTE, increased risk of serious adverse events appeared to be primarily driven by a higher rate of VTE in patients treated with bevacizumab.² Other high quality systematic reviews reported similar outcomes, with no difference in clinical efficacy or safety between bevacizumab or ranibizumab treatment for neovascular AMD.^{8,21}

In 2016, a systematic review evaluated safety and efficacy of anti-VEGF agents for the treatment of neovascular AMD.¹ Outcomes examined included visual acuity (measured by the change in ETDRS letters), quality of life and adverse events (especially thrombotic events, infection, bleeding, and death) at 1 and 2 years.¹ Five publications from 4 studies evaluated efficacy of bevacizumab versus ranibizumab.¹ Data from these trials were not pooled in a meta-analysis, but overall, there was no difference between groups in the proportion of patients with clinically significant vision changes (> 15 letters on the ETDRS chart) or mean change in best-corrected visual acuity score (low quality evidence).¹ Similarly, in trials which reported adverse effects, there was no difference in risk of death, arterial thrombotic events (including MI or stroke), endophthalmitis or infection.¹ Adverse events that were more common with bevacizumab than ranibizumab included serious systemic adverse events (40% vs 32%, RR 1.30, 95% CI 1.07 to 1.57; p=0.009; NNH=12, 1 RCT for 2 years), and serious ocular events at 12 to 18 months (3 vs 1%, RR 2.77, 95% CI 1.18 to 6.54; p=NR; NNH=50, 3 RCTs).¹ Serious systemic adverse events included hypertension, arteriothrombotic events, systemic hemorrhage, congestive heart failure, VTE, or vascular death.²² Specific ocular events included endophthalmitis, uveitis, retinal/choroidal detachment, retinal tear, ocular vessel embolism or occlusion and vitreous hemorrhage.¹ Evidence from 7 RCTs evaluated different dosing regimens of ranibizumab. Regimens included doses of 0.3 mg, 0.5 mg, and 2 mg administered monthly, quarterly, or on an as needed basis over the course of 1 to 2 years.¹ Overall, there was insufficient evidence to assess changes in vision or serious adverse effects with different dosing regimens due to lack of reported comparative outcomes.¹ Low quality evidence from 1 RCT (n=353) indicates that fixed monthly regimens of 0.3 mg may be more effective than quarterly injections of 0.3 mg (MD -3.9 letters, 95% CI -7.7 to -0.9) or 0.5 mg (MD -5.2 letters, 95% CI -8.6 to -1.7) ranibizumab.¹ The proportion of patients who had an improvement of greater than 15 ETDRS letters was 14% in patients given quarterly injections compared to 29% with monthly injections.¹ Similarly, 8% of patients given 0.3 mg quarterly compared to 3% receiving 0.3 mg monthly injections progressed to legal blindness (20/200) in 12 months.¹ Statistical significance for these outcomes was not reported.¹ Evidence from 2 RCTs compared aflibercept to ranibizumab.¹ Overall, aflibercept and ranibizumab demonstrated similar efficacy in the mean change in best-corrected visual acuity and proportion of patients with a gain of 15 or more ETDRS letters (moderate quality evidence).¹ Adverse events were similar between groups though events were infrequent and studies were not powered to evaluate these outcomes.¹ There was insufficient evidence evaluating differences in dosing regimens of aflibercept (given monthly or every 2 months).¹ Evidence comparing different regimens of bevacizumab (either monthly or as needed dosing) was limited to 2 RCTs.¹ Overall, changes in visual acuity were similar between groups, though statistical significance was not assessed for the majority of outcomes (low quality evidence).¹ There was no comparative data on adverse effects between patients taking bevacizumab monthly or as needed.¹ Authors do note that bevacizumab is not formulated for intravitreal injections and requires compounding which may increase risk of infections due to potential contamination.¹

Two systematic reviews have examined comparative efficacy and safety of different dosing regimens of ranibizumab in neovascular AMD.^{8,23} Patients in these reviews were treated with injections of 0.5 mg ranibizumab on a scheduled basis or with a 1-3 months of scheduled doses followed by as needed treatment for patients with progressive disease.⁸ The efficacy of ranibizumab when given alone or in conjunction with photodynamic therapy was also examined.⁸ Evidence examining difference in ranibizumab regimens included data from 6 RCTs.⁸ Patients were on average 73 to 80 years of age and were followed for 1 to 2 years.⁸

The authors found a slight statistical benefit when ranibizumab was administered as needed compared to a scheduled regimen (2 RCTs, weighted MD 1.97 letters, 95% CI 0.14 to 3.794, $p=0.04$, $I^2=0\%$) and combination treatment of ranibizumab plus photodynamic therapy versus ranibizumab alone (4 RCTs, weighted MD 2.74, 95% CI 0.26 to 5.21, $p=0.03$, $I^2=0\%$), though differences were not clinically significant.⁸ Another systematic review which examined differences in dosing regimens of ranibizumab (either scheduled monthly doses or therapy given as needed depending on disease progression) reached similar conclusions.²³ The meta-analysis included similar studies (3 RCTs, $n=1844$) and found no clinical difference in best corrected visual acuity between groups after 2 years (weighted MD 1.9, 95% CI 0.5 to 3.3, $p=0.008$, $I^2=0\%$).²³ At 2 years, the total number of intravitreal injections was significantly less in patients treated on an as needed basis compared to patients receiving scheduled monthly therapy (MD 8.4, 95% CI 7.9 to 8.9, $p<0.00001$, $I^2=95\%$).²³ Heterogeneity between these trials was significant, but results all demonstrated consistently fewer injections when therapy was given as needed.

A Cochrane review in 2016 examined the efficacy of anti-VEGF agents for the treatment of choroidal neovascularization due to pathological myopia.⁷ The review included 6 RCTs or quasi-RCTs ($n=594$) which compared anti-VEGF agents to photodynamic therapy, placebo, or other anti-VEGF agents.⁷ Direct comparative evidence between anti-VEGF agents was limited to 2 trials which evaluated bevacizumab and ranibizumab.⁷ Treatment was primarily given as 1 injection followed by as needed treatment depending on disease activity upon optical imaging.⁷ Compared to photodynamic therapy, the current standard of care, anti-VEGF agents improved mean visual acuity by approximately 7 and 13 ETDRS letters at 1 and 2 years, respectively.⁷ The proportion of patients achieving a clinically significant improvement in visual acuity (corresponding to >3 ETDRS lines) was also greater in patients given anti-VEGF agents after 1 year (RR 1.86, 95% CI 1.27 to 2.73, 226 people, moderate quality evidence) and 2 years of treatment (RR 3.43, 95% CI 1.37 to 8.56, 92 people, low quality evidence) compared to those receiving photodynamic therapy.⁷ In 1 of these trials, patients in the control groups were allowed to receive anti-VEGF treatment after 3 months, which may lead to a more conservative estimate of efficacy.⁷ Similar improvements were seen with bevacizumab compared to laser photocoagulation therapy with mean improvements of approximately 11 and 14 ETDRS letters after 1 and 2 years (low quality evidence).⁷ In 2 RCTs directly comparing bevacizumab and ranibizumab, there was no difference in change in visual acuity after 1 year (RR 0.79, 95% CI 0.50 to 1.27, $P=0.33$, moderate quality evidence).⁷ Adverse events were rarely reported, and no serious adverse events occurred in patients randomized to control groups.⁷ Differences in adverse events failed to achieve statistical significance, though adverse events were more common in patients treated with anti-VEGF therapy (RR 1.82, 95% CI 0.23 to 14.71, $p=0.14$). Serious systemic adverse events occurred in 15 patients (4.2%) taking anti-VEGF agents, and ocular adverse events occurred in 5 patients (1.4%).⁷

Similar results were documented in another systematic review of anti-VEGF agents for the treatment of choroidal neovascularization in conditions unrelated to AMD.²⁴ This review included both RCTs and comparative non-randomized trials. Of the 16 included studies, 13 ($n=1017$) were in patients with myopic choroidal neovascularization.²⁴ The majority of patients included in these trials were female and 35 to 67 years of age.²⁴ Mean baseline best corrected visual acuity was between 81 and 99 letters.²⁴ Three study regimens required 3 monthly loading doses and continued treatment in all studies was based on clinical assessment at follow-up visits.²⁴ Patients received an average of 1.6 to 4.72 injections over the course of these studies.²⁴ Due to significant heterogeneity between studies, results were not pooled in a meta-analysis. However, in myopic choroidal neovascularization, the proportion of patients with a clinical improvement of greater than 15 letters ranged from 27% to 70% in patients taking anti-VEGF therapy compared to 14% to 20% in patients given photodynamic therapy.²⁴ Evidence was limited by quality of the included trials, limited population size, and significant methodological heterogeneity between studies.²⁴ Differences in baseline visual acuity and treatment regimens may have contributed to the wide difference in treatment outcomes. In trials directly comparing bevacizumab and ranibizumab, no statistical difference in best corrected visual acuity was reported between groups.²⁴

A systematic review examined safety of anti-VEGF agents in patients with diabetic macular edema and consistent exposure to anti-VEGF agents (i.e. receiving monthly injections for at least 2 years).²⁵ Four RCTs ($n=1078$) of aflibercept and ranibizumab versus sham treatment were included in the review.²⁵ Outcomes examined included risk of MI, CVA, VTE, and mortality.²⁵ The mean age of patients enrolled in trials was 61 to 64 years.²⁵ Baseline cardiovascular risk

factors were not evaluated, though patients with recent stroke or MI (within 3 to 6 months) were excluded from these trials.²⁵ Compared to sham-laser treatment, patients treated with anti-VEGF therapy had a higher risk of all-cause mortality (OR 2.57, 95% CI 1.31 to 5.05, p=0.006), CVA (OR 2.33, 95% CI 1.04 to 5.22), and vascular-related death (OR 2.23, 95% CI 1.01 to 4.89, p=0.05).²⁵ Risk for VTE and MI failed to achieve statistical significance.²⁵ All outcomes were graded as moderate quality evidence.²⁵ In addition, similar outcomes were observed in subgroup analyses of ranibizumab 0.5 mg and 0.3 mg doses, and no difference was observed between patients receiving either ranibizumab or aflibercept.²⁵

A systematic review published in 2016 examined the comparative efficacy and safety of anti-VEGF agents in patients with diabetic macular edema. The review included updated evidence from 8 systematic reviews and 4 RCTs.⁵ Overall, due to quality of included trials and lack of direct comparative data, evidence for improvements in visual acuity was graded as low quality.⁵ Overall, authors concluded that in patients with good baseline visual acuity (>69 ETDRS letters), ranibizumab, aflibercept, and bevacizumab were equally effective at improving visual acuity at 6 to 12 months.⁵ Results from 1 RCT indicate that in patients with worse baseline visual acuity (<69 ETDRS letters), aflibercept may have improved visual acuity at 1 year compared to ranibizumab or bevacizumab (MD 4.7 and 6.5 letters, respectively).⁵ The clinical significance of these differences remains unclear. Regarding adverse effects, there were no significant differences between agents.⁵ However, studies were not powered to examine these rare events and many studies excluded patients at high risk for thrombotic events.⁵ Authors note that all intravitreal injections have an increased risk of endophthalmitis with reported rates of 0.05 to 1.6%, but direct comparative evidence between agents is lacking.⁵

New Guidelines:

Guidance from the National Institute for Health and Care Excellence (NICE) for the use of aflibercept in patients with diabetic macular edema was published in 2015.²⁶ Recommendations were based on evidence from 2 RCTs evaluating change in best corrected visual acuity at 1 year.²⁶ The clinical and cost effectiveness was evaluated in the total population and in subgroups of patients with prior cataract surgery and baseline central retinal thickness less than 400 micrometers.²⁶ Clinically, aflibercept demonstrated a significant improvement in the best corrected visual acuity compared to laser photocoagulation when given every 4 or 8 weeks.²⁶ Subgroup analyses demonstrated that in patients with a central retinal thickness of less than 400 micrometers, differences failed to achieve statistical significance.²⁶ The analysis was limited due to the small population of patients with central retinal thickness less than 400 micrometers (n=78) and lack of balanced baseline characteristics in this subgroup.²⁶ Based on cost-effectiveness results, NICE guidance recommends initiation of aflibercept only in patients with a central retinal thickness greater than 400 micrometers.²⁶

In the past few years, the American Academy of Ophthalmology has updated guidelines on the use of anti-VEGF agents in retinal vein occlusion, neovascular AMD and diabetic retinopathy. Guidelines recommend anti-VEGF agents as a first-line therapy for the treatment of macular edema associated with branched or central retinal vein occlusion (strong recommendation based on good quality evidence).¹⁹ No specific recommendations are made for any particular agent. Intraocular steroids have also demonstrated benefit in treatment of macular edema due to retinal vein occlusion and are recommended as a second-line treatment due to their associated with increased risk of cataracts and glaucoma (strong recommendation based on good quality evidence).¹⁹ Similar recommendations are made in guidelines for the treatment of neovascular AMD.¹³ Anti-VEGF agents are recommended as first-line therapy in patients with neovascular AMD (strong recommendation based on good quality evidence), but no recommendations are made for any particular agent or treatment regimen.¹³ Guidelines for diabetic retinopathy state anti-VEGF agents may be used for the treatment of retinopathy associated with clinically significant macular edema regardless of retinopathy severity (strong recommendation based on good quality evidence).¹⁵ Anti-VEGF agents are first-line therapy in patients with central macular edema.¹⁵ They may be used as monotherapy or in combination with focal laser treatment or panretinal photocoagulation.¹⁵ Anti-VEGF agents are not recommended for treatment of mild or moderate severity retinopathy alone (strong recommendation based on good quality evidence).¹⁵ Though

evidence is limited, treatment may be considered in patients with high-risk proliferative diabetic retinopathy with or without macular edema (strong recommendation based on observational studies).¹⁵ Guidelines note that treatment decision should be based on the individual risks and benefits of the patient.¹⁵

New Formulations or Indications:

In 2016, bevacizumab labeling was updated to include a new indication for treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer either in combination with carboplatin and paclitaxel, in combination with carboplatin and gemcitabine, and as monotherapy following combination therapy.²⁷

Since 2015, aflibercept and ranibizumab were FDA-approved for treatment of diabetic retinopathy in patients with diabetic macular edema, and ranibizumab achieved approval for the treatment of myopic choroidal neovascularization.^{20,28}

A new formulation for pre-filled 0.5 mg syringes of ranibizumab was also approved in 2015.²⁰

New FDA Safety Alerts:

In 2016, labeling for aflibercept was updated to include contraindications for hypersensitivity reactions including rash, pruritus, urticarial, or severe anaphylactic/anaphylactoid reactions.²⁷

Randomized Controlled Trials:

A total of 324 citations were manually reviewed from the initial literature search. After further review, 314 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). If multiple publications presented results from the same trial, the publication with the most recent results and longest follow-up was included. Data supporting the use of aflibercept and ranibizumab for recently FDA-approved indications of diabetic retinopathy in patients with diabetic macular edema and for ranibizumab in patients with treatment of myopic choroidal neovascularization are also included. The remaining 10 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Berg K, et al. 2016. ²⁹ DB, MC, NI, RCT Duration: 2 years N=441	1. Ranibizumab 0.5 mg 2. Bevacizumab 1.25 mg T&E protocol: Intravitreal injections given monthly until achievement of inactive disease then injections were extended by 2 weeks at a time up to 12 weeks. Treatment periods were shortened in 2 week periods with disease recurrence.	Treatment naïve adults >50 years of age with neovascular AMD and BCVA between 20/25 and 20/320.	Mean change in BCVA at 2 years (measured by ETDRS chart)	Ranibizumab: 6.6 letters (SD 15.2) Bevacizumab: 7.4 letters (SD 16.0) MD 0.8 letters (95% CI -4.1 to 2.5; p=0.634)

<p>Chakravarthy U, et al. 2015.³⁰</p> <p>MC, NI, RCT</p> <p>Duration: 2 years</p> <p>N=628</p>	<ol style="list-style-type: none"> 1. Ranibizumab 0.5 mg continuous monthly intravitreal injections 2. Ranibizumab 0.5 mg intravitreal injections for 3 months followed by retreatment with active disease 3. Bevacizumab 1.25 mg continuous monthly intravitreal injections 4. Bevacizumab 1.25 mg intravitreal injections for 3 months followed by retreatment with active disease 	<p>Treatment naïve adults ≥50 years of age with neovascular AMD and BCVA ≥25 letters</p>	<p>BCVA at 2 years</p>	<p>Ranibizumab (Groups 1 and 2): 67.8 letters (SD 17.0) Becavizumab (Groups 3 and 4): 66.1 letters (SD 18.4) MD -1.37 letters (95% CI -3.75 to 1.01; p=0.26)</p> <p>Continuous treatment (Groups 1 and 3): 66.6 (SD 17.9) Retreatment upon disease recurrence (Groups 2 and 4): 37.3 (SD 17.5) MD -1.63 letters (95% CI -4.01 to 0.75; p=0.18)</p>
<p>Wiley HE, et al. 2016.³¹</p> <p>DB, 3-month crossover, RCT</p> <p>Duration: 9 months</p> <p>N=56</p>	<ol style="list-style-type: none"> 1. Ranibizumab 0.3 mg monthly 2. Bevacizumab 1.25 mg monthly 	<p>Adults with type 1 or 2 diabetes and DME</p>	<p>Mean change in BCVA (ETDRS chart) at 3 months</p>	<p>Ranibizumab: 6.6 letters (95% CI 4.5 to 8.7) Becavizumab: 5.3 letters (95% CI 3.2 to 7.4)</p> <p>MD 1.3 letters (95% CI 0.07 to 2.5; P=0.039)</p>
<p>Wells JA, et al. 2016.⁶</p> <p>MC, NI, RCT</p> <p>Duration: 2 years</p> <p>N=660</p>	<ol style="list-style-type: none"> 1. Aflibercept 2.0 mg 2. Bevacizumab 1.25 mg 3. Ranibizumab 0.3 mg <p>Treatment was given monthly for 12 months then every 1-4 months thereafter depending on disease stability. Addition of focal grid laser photocoagulation could be added at 6 months with persistent disease activity.</p>	<p>Adults with DME and BCVA of 20/32 to 20/320 on the Snellen chart</p>	<p>Mean change in visual acuity at 2 years (post-hoc exploratory analysis)</p>	<ol style="list-style-type: none"> 1. Aflibercept 12.8 letters (SD 12.4) 2. Bevacizumab 10.0 letters (SD 11.8) 3. Ranibizumab 12.3 letters (SD 10.5) <p>Aflibercept vs. bevacizumab: MD 2.7 (95% CI 0.3 to 5.2; P=0.02) Aflibercept vs. ranibizumab: MD 0.7 (95% CI -1.3 to 2.8; P=0.47) Ranibizumab vs. bevacizumab: MD 2.0 (95% CI -0.4 to 4.4; P=0.11)</p>
<p>Bressler SB, et al. 2016.³²</p> <p>DB, MC, RCT</p> <p>Duration: 5 years</p> <p>N=450</p>	<ol style="list-style-type: none"> 1. Laser photocoagulation + very deferred ranibizumab (1.5 to 3 years later) 2. Ranibizumab + prompt laser photocoagulation 3. Laser photocoagulation + triamcinolone + very deferred ranibizumab (1.5 to 3 years later) 4. Ranibizumab + deferred laser photocoagulation (≥6 months later) 	<p>Adults with DME and BCVA of 20/32 to 20/320 on the Snellen chart</p>	<p>Mean change in BCVA at 5 years (post-hoc exploratory analysis)</p>	<ol style="list-style-type: none"> 1. 5 letters (SD 14) 2. 8 letters (SD 13) 3. 7 letters (SD 14) 4. 10 letters (SD 13) <p>Compared to ranibizumab + deferred laser</p> <ol style="list-style-type: none"> 1. MD 4.4 (95% CI 1.2 to 7.6; p=0.001) 2. MD 2.0 (95% CI -1.6 to 5.7; p=0.186)

				3. MD 2.8 (95% CI -0.9 to 6.5; p=0.067)
Pece A, et al. 2015. ³³ RCT Mean duration: 19 months N=80	1. Bevacizumab 0.5 mg 2. Ranibizumab 1.25 mg Treatment was once then as needed upon presence of active lesions, progressive disease, or worsening of BCVA >1 line (5 letters)	Adults with myopic CNV and BCVA >20/400 on the Snellen chart	Mean change in BCVA	Bevacizumab: 55 letters (SD 26) Ranibizumab: 58 letters (SD 21) OR 2.46 (95% CI 0.88 to 6.83; p=0.138)
Brown DM, et al. 2015. ³⁴ DB, MC, RCT Duration: 2 years N=466	1. Aflibercept 2 mg every 4 weeks 2. Aflibercept 2 mg every 8 weeks after 5 monthly doses 3. Macular laser photocoagulation at baseline and upon follow-up if clinically significant macular edema was present	Adults with retinopathy, DME and BCVA of 73-24 letters (20/40 to 20/320)	Proportion of patients with ≥ 2 step improvement in the DRSS score (pre-specified exploratory outcome)	1. 37.0% (95% CI NR); p<0.0001 vs. laser 2. 37.1% (95% CI NR); p<0.0001 vs. laser 3. 15.6% (95% CI NR) Aflibercept vs. laser photocoagulation ARR 22%, NNT=5
Brown DM, et al. 2015. ³⁴ DB, MC, RCT Duration: 2 years N=406	1. Aflibercept 2 mg every 4 weeks 2. Aflibercept 2 mg every 8 weeks after 5 monthly doses 3. Macular laser photocoagulation at baseline and upon follow-up if clinically significant macular edema was present	Adults with retinopathy, DME and BCVA of 73-24 letters (20/40 to 20/320)	Proportion of patients with ≥ 2 step improvement in the DRSS score (pre-specified exploratory outcome)	1. 29.3% (95% CI NR); p=0.0004 vs. laser; ARR 21.1%, NNT=5 2. 32.6%(95% CI NR); p<0.0001 vs. laser; ARR 24.4%, NNT=4 3. 8.2%
Ip MS, et al. 2015. ¹⁶ DB, MC, RCT Duration: 3 years N=759	1. Ranibizumab 0.3 mg monthly 2. Ranibizumab 0.5 mg monthly 3. Sham injections monthly Patients randomized to sham injections could receive ranibizumab 0.5 mg monthly after 25 months	Adults with retinopathy, DME and BCVA of 20/40 to 20/320	Proportion of patients with ≥ 2 or ≥3 step improvement in the DRSS score (post-hoc exploratory outcome)	1. 38.9% (95% CI NR); p<0.0001 vs. sham injections 2. 39.3% (95% CI NR); p<0.0001 vs. sham injections 3. 23.8% (95% CI NR) Ranibizumab vs: sham injections ARR 15%, NNT=7
Wolf S, et al. 2014. ³⁵	1. Ranibizumab 0.5 mg on day 1 and at 1 month with further treatment based on change in VA	Adults with myopic CNV and BCVA of	Mean change in BCVA at 1-3 months (ETDRS letters)	1. 10.5 letters (SD 8.2), p<0.00001 vs. verteporfin photodynamic therapy 2. 10.6 letters (SD 7.3), p<0.00001 vs. verteporfin photodynamic therapy

Phase 3, Superiority and NI, DB, MC, RCT	2. Ranibizumab 0.5 mg on Day 1 with further treatment based on presence of active disease upon exam	24-78 ETDRS letters		3. 2.2 letters (SD 9.5)
Duration: 1 year N=244	3. Verteporfin photodynamic therapy on Day 1 with further treatment based on active disease upon exam. Cross-over treatment with ranibizumab was permitted after 3 months.			Noninferiority between ranibizumab groups achieved

Abbreviations: AMD = age-related macular degeneration; ARR = absolute risk reduction; BCVA = best corrected visual acuity; CNV= choroidal neovascularization; DB = double blind; DME = diabetic macular edema; DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; MC = multicenter; MD = mean difference; NI = noninferiority; NNT = number needed to treat; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; SD = standard deviation

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Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INTRAVEN	VIAL	AVASTIN	BEVACIZUMAB	Y
INTRAOCULR	SYRINGE	MACUGEN	PEGAPTANIB SODIUM	N
INTRAOCULR	VIAL	EYLEA	AFLIBERCEPT	N
INTRAOCULR	SYRINGE	BEVACIZUMAB	BEVACIZUMAB	N
INTRAOCULR	VIAL	LUCENTIS	RANIBIZUMAB	N
INTRAOCULR	VIAL	LUCENTIS	RANIBIZUMAB	N

Appendix 2: Abstracts of Comparative Clinical Trials

Berg K, et al. 2016.²⁹

Ranibizumab or Bevacizumab for Neovascular Age-Related Macular Degeneration According to the Lucentis Compared to Avastin Study Treat-and-Extend Protocol: Two-Year Results

Purpose: To compare the efficacy and safety of bevacizumab (Avastin; F. Hoffmann-La Roche Ltd, Basel, Switzerland) versus ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland) for neovascular age-related macular degeneration (nAMD) after 2 years when using a treat-and-extend protocol. **Design:** Multicenter, randomized, noninferiority trial with a noninferiority limit of 5 letters. **Participants:** Patients 50 years of age or older with previously untreated nAMD in 1 eye and best-corrected visual acuity 20/25 to 20/320. **Methods:** Patients were assigned randomly to receive intravitreal injections with either ranibizumab 0.5 mg or bevacizumab 1.25 mg. Injections were given every 4 weeks until inactive disease was achieved. The treatment interval then was extended by 2 weeks at a time up to a maximum of 12 weeks. In the event of a recurrence, the treatment interval was shortened by 2 weeks at a time. **Main Outcome Measure:** Mean change in visual acuity at 2 years. **Results:** Of a total of 441 randomized patients, 339 patients (79%) completed the 2-year visit. According to perprotocol analysis at 2 years, bevacizumab was equivalent to ranibizumab, with 7.4 and 6.6 letters gained, respectively (95% confidence interval [CI] of mean difference, 4.1 to 2.5; $P=0.634$). Intention-to-treat analysis was concordant, with a gain of 7.8 letters for bevacizumab and 7.5 letters for ranibizumab (95%CI of mean difference, 3.2 to 2.7; $P=0.873$). The 2-year results did not show any significant difference in mean central retinal thickness, with a decrease of 113 μm for bevacizumab and 122 μm for ranibizumab (95%CI of mean difference, 32 to 15; $P=0.476$). There was a statistically significant difference between the drugs regarding the number of treatments given, with 18.2 injections for bevacizumab and 16.0 injections for ranibizumab (95%CI of mean difference, 3.4 to 1.0; $P<0.001$). The number of serious adverse events was similar between the groups over the course of the study. **Conclusions:** At 2 years, bevacizumab and ranibizumab had an equivalent effect on visual acuity and reduction of central retinal thickness when administered according to a treat-and-extend protocol for nAMD. There was no significant difference in the number of serious adverse events between the treatment groups.

Chakravarthy U, et al. 2015.³⁰

A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN)

Background: Bevacizumab (Avastin®, Roche), which is used in cancer therapy, is the 'parent' molecule from which ranibizumab (Lucentis®, Novartis) was derived for the treatment of neovascular age-related macular degeneration (nAMD). There were reports in the literature on the effectiveness of bevacizumab in treating nAMD, but no trials. The cost per dose of bevacizumab is about 5–10% that of ranibizumab. This trial was a head-to-head comparison of these two drugs.

Objective: To compare the clinical effectiveness and cost-effectiveness of ranibizumab and bevacizumab, and two treatment regimens, for nAMD.

Design: Multicentre, factorial randomised controlled trial with within-trial cost-utility and cost-minimisation analyses from the perspective of the UK NHS.

Participants, health professionals and researchers were masked to allocation of drug but not regimen. Computer-generated random allocations to combinations of ranibizumab or bevacizumab, and continuous or discontinuous regimen, were stratified by centre, blocked and concealed.

Setting: Twenty-three ophthalmology departments in NHS hospitals

Participants: Patients ≥ 50 years old with active nAMD in the study eye with best corrected distance visual acuity (BCVA) ≥ 25 letters measured on a Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. Previous treatment for nAMD, long-standing disease, lesion diameter $> 6000 \mu\text{m}$, thick blood at the fovea and any other confounding ocular disease were exclusion criteria. One eye per participant was studied; the fellow eye was treated according to usual care, if required.

Author: Servid

Date: May 2017

Interventions: Ranibizumab and bevacizumab were procured commercially. Doses were ranibizumab 0.5 mg or bevacizumab 1.25 mg. The repackaged bevacizumab was quality assured. All participants were treated at visits 0, 1 and 2. Participants randomised to the continuous regimen were treated monthly thereafter. Participants randomised to the discontinuous regimen were not retreated after visit 2 unless pre-specified criteria for active disease were met. If retreatment was needed, monthly injections over 3 months were mandated.

Main outcome measures: The primary outcome was BCVA. The non-inferiority margin was 3.5 letters. Secondary outcomes were contrast sensitivity; near visual acuity; reading index; neovascular lesion morphology; generic and disease-specific patient-reported outcomes, including macular disease-specific quality of life; survival free from treatment failure; resource use; quality-adjusted life-years (QALYs); and development of new geographic atrophy (GA) (outcome added during the trial). Results are reported for the study eye, except for patient-reported outcomes.

Results: Between 27 March 2008 and 15 October 2010, 610 participants were allocated and treated (314 ranibizumab, 296 bevacizumab; at 3 months, 305 continuous, 300 discontinuous). After 2 years, bevacizumab was neither non-inferior nor inferior to ranibizumab [−1.37 letters, 95% confidence interval (CI) −3.75 to +1.01 letters] and discontinuous treatment was neither non-inferior nor inferior to continuous treatment (−1.63 letters, 95% CI −4.01 to +0.75 letters). Lesion thickness at the fovea was similar by drug [geometric mean ratio (GMR) 0.96, 95% CI 0.90 to 1.03; $p = 0.24$] but 9% less with continuous treatment (GMR 0.91, 95% CI 0.85 to 0.97; $p = 0.004$). Odds of developing new GA during the trial were similar by drug [odds ratio (OR) 0.87, 95% CI 0.61 to 1.25; $p = 0.46$] but significantly higher with continuous treatment (OR 1.47, 95% CI 1.03 to 2.11; $p = 0.033$). Safety outcomes did not differ by drug but mortality was lower with continuous treatment (OR 0.47, 95% CI 0.22 to 1.03; $p = 0.05$). Continuous ranibizumab cost £3.5M per QALY compared with continuous bevacizumab; continuous bevacizumab cost £30,220 per QALY compared with discontinuous bevacizumab. These results were robust in sensitivity analyses.

Conclusions: Ranibizumab and bevacizumab have similar efficacy. Discontinuing treatment and restarting when required results in slightly worse efficacy. Safety was worse with discontinuous treatment, although new GA developed more often with continuous treatment. Ranibizumab is not cost-effective, although it remains uncertain whether or not continuous bevacizumab is cost-effective compared with discontinuous bevacizumab at £20,000 per QALY threshold. Future studies should focus on the ocular safety of the two drugs, further optimisation of treatment regimens and criteria for stopping treatment.

Wiley HE, et al. 2016.³¹

A 36-Week Randomized Trial of Bevacizumab and Ranibizumab for Diabetic Macular Edema

Purpose: To investigate the comparative efficacy of bevacizumab (Avastin) and ranibizumab (Lucentis; both Genentech, Inc, South San Francisco, CA) for diabetic macular edema (DME) using a crossover study design. Design: Randomized, double-masked, 36-week, 3-period crossover clinical trial. Participants: Fifty-six subjects with DME involving the center of the macula in one or both eyes. Methods: Monthly intravitreal injections of bevacizumab (1.25 mg) or ranibizumab (0.3 mg). Main Outcome Measures: Comparison of mean changes in visual acuity and central retinal thickness, tested using a linear mixed-effects model. Results: Based on the linear mixed-effects model, the 3-month estimated mean improvement in visual acuity was 5.3 letters for bevacizumab and 6.6 letters for ranibizumab (difference, 1.3 letters; $P = 0.039$). Estimated change in optical coherence tomography (OCT) central subfield mean thickness (CSMT) was 89 μm for bevacizumab and 137 μm for ranibizumab (difference, 48 μm ; $P < 0.001$). Incorporating cumulative treatment benefit, the model yielded a predicted 36-week (9-month) average improvement in visual acuity of 7.1 letters (95% confidence interval [CI], 5.0e9.2) for bevacizumab and 8.4 letters (95% CI, 6.3e10.5) for ranibizumab, and a change in OCT CSMT of 128 μm (95% CI, 155 to 100) for bevacizumab and 176 μm (95% CI, 202 to 149) for ranibizumab. There was no significant treatment-by-period interaction (i.e., treatment difference was constant in all 3 periods), nor was there a significant differential carryover effect from one period to the next. Conclusions: This trial demonstrated a statistically significant but small relative clinical benefit of ranibizumab compared with bevacizumab for treatment of DME, using a markedly reduced sample size relative to a full comparative efficacy study. The effects on visual acuity and central retinal thickness for the 2 drugs are consistent with those reported at 1 year for the concurrent parallel-group trial by the Diabetic Retinopathy Clinical Research

Network testing bevacizumab, ranibizumab, and aflibercept for DME. The 3-period crossover design allowed for meaningful and efficient comparison, suggesting that this approach may be useful for future comparative efficacy studies of anti-vascular endothelial growth factor drugs for DME.

Wells JA, et al. 2016.⁶

Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial

Purpose: To provide 2-year results comparing anti-vascular endothelial growth factor (VEGF) agents for center-involved diabetic macular edema (DME) using a standardized follow-up and retreatment regimen. **Design:** Randomized clinical trial. **Participants:** Six hundred sixty participants with visual acuity (VA) impairment from DME. **Methods:** Randomization to 2.0-mg aflibercept, 1.25-mg repackaged (compounded) bevacizumab, or 0.3mg ranibizumab intravitreal injections performed up to monthly using a protocol-specific follow-up and retreatment regimen. Focal/grid laser photocoagulation was added after 6 months if DME persisted. Visits occurred every 4 weeks during year 1 and were extended up to every 4 months thereafter when VA and macular thickness were stable. **Main Outcome Measures:** Change in VA, adverse events, and retreatment frequency. **Results:** Median numbers of injections were 5, 6, and 6 in year 2 and 15, 16, and 15 over 2 years in the aflibercept, bevacizumab, and ranibizumab groups, respectively (global $P \geq 0.08$). Focal/grid laser photocoagulation was administered in 41%, 64%, and 52%, respectively (aflibercept vs. bevacizumab, $P < 0.001$; aflibercept vs. ranibizumab, $P \geq 0.04$; bevacizumab vs. ranibizumab, $P \geq 0.01$). At 2 years, mean VA improved by 12.8, 10.0, and 12.3 letters, respectively. Treatment group differences varied by baseline VA ($P \geq 0.02$ for interaction). With worse baseline VA (20/50 to 20/320), mean improvement was 18.1, 13.3, and 16.1 letters, respectively (aflibercept vs. bevacizumab, $P \geq 0.02$; aflibercept vs. ranibizumab, $P \geq 0.18$; ranibizumab vs. bevacizumab, $P \geq 0.18$). With better baseline VA (20/32 to 20/40), mean improvement was 7.8, 6.8, and 8.6 letters, respectively ($P > 0.10$, for pairwise comparisons). Anti-Platelet Trialists' Collaboration (APTCC) events occurred in 5% with aflibercept, 8% with bevacizumab, and 12% with ranibizumab (global $P \geq 0.047$; aflibercept vs. bevacizumab, $P \geq 0.34$; aflibercept vs. ranibizumab, $P \geq 0.047$; ranibizumab vs. bevacizumab, $P \geq 0.20$; global $P \geq 0.09$ adjusted for potential confounders). **Conclusions:** All 3 anti-VEGF groups showed VA improvement from baseline to 2 years with a decreased number of injections in year 2. Visual acuity outcomes were similar for eyes with better baseline VA. Among eyes with worse baseline VA, aflibercept had superior 2-year VA outcomes compared with bevacizumab, but superiority of aflibercept over ranibizumab, noted at 1 year, was no longer identified. Higher APTCC event rates with ranibizumab over 2 years warrants continued evaluation in future trials.

Bressler SB, et al. 2016.³²

Five-Year Outcomes of Ranibizumab With Prompt or Deferred Laser Versus Laser or Triamcinolone Plus Deferred Ranibizumab for Diabetic Macular Edema

PURPOSE: To compare long-term vision and anatomic effects of ranibizumab with prompt or deferred laser vs laser or triamcinolone D laser with very deferred ranibizumab in diabetic macular edema (DME). **DESIGN:** Randomized clinical trial. **METHODS:** Eight hundred and twenty-eight study eyes (558 [67%] completed the 5-year visit), at 52 sites, with visual acuity 20/32 to 20/320 and DME involving the central macula were randomly assigned to intravitreal ranibizumab (0.5 mg) with either (1) prompt or (2) deferred laser; (3) sham injection D prompt laser; or (4) intravitreal triamcinolone (4 mg) D prompt laser. The latter 2 groups could initiate ranibizumab as early as 74 weeks from baseline, for persistent DME with vision impairment. The main outcome measures were visual acuity, optical coherence central subfield thickness, and number of injections through 5 years. **RESULTS:** At 5 years mean (\pm standard deviation) change in Early Treatment Diabetic Retinopathy Study visual acuity letter scores from baseline in the ranibizumab D deferred laser (N=111), ranibizumab D prompt laser (N=124), laser/very deferred ranibizumab (N=198), and triamcinolone D laser/very deferred ranibizumab (N=125) groups were 10 ± 13 , 8 ± 13 , 5 ± 14 , and 7 ± 14 , respectively. The difference (95% confidence interval) in mean change between ranibizumab D deferred laser and laser/very deferred ranibizumab and triamcinolone D laser/very deferred ranibizumab was 4.4 (1.2–7.6, $P < 0.001$) and 2.8 (0.9 to 6.5, $P = 0.067$), respectively, at 5 years. **CONCLUSIONS:** Recognizing

limitations of follow-up available at 5 years, eyes receiving initial ranibizumab therapy for center-involving DME likely have better long-term vision improvements than eyes managed with laser or triamcinolone D laser followed by very deferred ranibizumab for persistent thickening and vision impairment.

Pece A, et al. 2015.³³

A randomized trial of intravitreal bevacizumab vs. ranibizumab for myopic CNV

Aims: The aim was to compare the efficacy of intravitreal therapy with bevacizumab and ranibizumab for choroidal neovascularization (CNV) in pathologic myopia (PM). **Methods:** This was a prospective multicenter randomized non-blinded trial. **Results:** In seven centers, 78 eyes were randomized 1:1 to treatment with bevacizumab (group B, 40 eyes) or ranibizumab (group R, 38 eyes) given with an “on demand” regimen (PRN). The mean follow-up was 19 months (SD 2, range 12–24). The mean BCVA at baseline was 0.60 logMAR (20/80 Snellen equivalent, Seq) and 50 letter score (ls). Mean final BCVA was 0.51 LogMAR (20/63 Seq) and 57 ls ($p=0.0009$ and $p=0.0002$, respectively). In group B, mean basal BCVA was 0.52 logMAR (20/63 Seq) and 54 ls, and final BCVA was 0.51 logMar (20/63 Seq) and 57 ls. In group R, mean basal BCVA was 0.62 logMAR (20/80 Seq) and 45 ls, and the final values were 0.50 logMAR (20/63 Seq) and 58 ls. Statistical comparison of the two groups showed no significant difference (logMAR $p=0.90$ and letters $p=0.78$). Multivariate analysis showed no influence of age or previous photodynamic treatment (PDT) on final visual changes. The mean number of treatments in the first year was 2.7 in group B and 2.3 in group R ($p=0.09$). **Conclusion:** Myopic CNV equally benefits from on-demand intravitreal injection of either bevacizumab or ranibizumab; the therapeutic effect is independent of previous PDT and age.

Brown 2015³⁴

Intravitreal Aflibercept for Diabetic Macular Edema 100-Week Results From the VISTA and VIVID Studies

Purpose: To compare efficacy and safety of 2 dosing regimens of intravitreal aflibercept injection (IAI) with macular laser photocoagulation for diabetic macular edema (DME). **Design:** Two similarly designed, randomized, phase 3 trials, VISTA^{DME} and VIVID^{DME}. **Participants:** Patients (eyes; $n=872$) with type 1 or 2 diabetes mellitus who had DME with central involvement. **Methods:** Eyes received IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 monthly doses (2q8), or laser control. **Main Outcome Measures:** The primary end point was mean change from baseline in best-corrected visual acuity (BCVA) at week 52. This report presents the 100-week results including mean change from baseline in BCVA, proportion of eyes that gained ≥ 15 letters, and proportion of eyes with a ≥ 2 -step improvement in the Diabetic Retinopathy Severity Scale (DRSS) score. **Results:** Mean BCVA gain from baseline to week 100 with IAI 2q4, IAI 2q8, and laser control was 11.5, 11.1, and 0.9 letters ($P < 0.0001$) in VISTA and 11.4, 9.4, and 0.7 letters ($P < 0.0001$) in VIVID, respectively. The proportion of eyes that gained ≥ 15 letters from baseline at week 100 was 38.3%, 33.1%, and 13.0% ($P < 0.0001$) in VISTA and 38.2%, 31.1%, and 12.1% ($P \leq 0.0001$) in VIVID. The proportion of eyes that lost ≥ 15 letters at week 100 was 3.2%, 0.7%, and 9.7% ($P \leq 0.0220$) in VISTA and 2.2%, 1.5%, and 12.9% ($P \leq 0.0008$) in VIVID. Significantly more eyes in the IAI 2q4 and 2q8 groups versus those in the laser control group had a ≥ 2 step improvement in the DRSS score in both VISTA (37.0% and 37.1% vs. 15.6%; $P < 0.0001$) and VIVID (29.3% and 32.6% vs. 8.2%; $P \leq 0.0004$). In an integrated safety analysis, the most frequent serious ocular adverse event was cataract (2.4%, 1.0%, and 0.3% for 2q4, 2q8, and control). **Conclusions:** In both VISTA and VIVID, the 52-week visual and anatomic superiority of IAI over laser control was sustained through week 100, with similar efficacy in the 2q4 and 2q8 groups. Safety in these studies was consistent with the known safety profile of IAI.

Ip MS, et al. 2015.¹⁶

Long-term Effects of Therapy with Ranibizumab on Diabetic Retinopathy Severity and Baseline Risk Factors for Worsening Retinopathy

Purpose: To assess the effects of intravitreal ranibizumab on diabetic retinopathy (DR) severity when administered for up to 3 years, evaluate the effect of delayed initiation of ranibizumab therapy on DR severity, and identify baseline patient characteristics associated with the development of proliferative DR (PDR).

Author: Servid

Date: May 2017

Design: Exploratory analyses of phase III, randomized, double-masked, sham-controlled multicenter clinical trials.

Participants: Adults with diabetic macular edema (DME) (N = 759), baseline best-corrected visual acuity 20/40 to 20/320 Snellen equivalent, and central foveal thickness ≥ 275 μ m.

Methods: Patients were randomized to monthly 0.3 or 0.5 mg ranibizumab or sham injections. Sham participants could switch to 0.5 mg ranibizumab during the third year (sham/0.5 mg crossover). Baseline risk factors were evaluated to explore potential associations with development of PDR. Time to first development of PDR was analyzed by Kaplan-Meier methods to calculate cumulative probabilities by group.

Main Outcome Measures: Study eye change on the Early Treatment Diabetic Retinopathy Study severity scale and a composite clinical outcome evaluating progression to PDR based on photographic changes plus clinically important events defining PDR.

Results: At month 36, a greater proportion of ranibizumab-treated eyes had ≥ 2 - or ≥ 3 -step DR improvement compared with sham/0.5 mg crossover. A ≥ 3 -step improvement was achieved at 36 months by 3.3%, 15.0%, and 13.2% of sham/0.5 mg, 0.3 mg, and 0.5 mg ranibizumab-treated eyes, respectively (P < 0.0001). Through 36 months, 39.1% of eyes in the sham/0.5 mg group developed PDR, as measured by composite outcome, compared with 18.3% and 17.1% of eyes treated with 0.3 or 0.5 mg ranibizumab, respectively. The presence of macular capillary nonperfusion at baseline seems to be associated with progression to PDR in ranibizumab treated eyes but did not meaningfully influence visual acuity improvement in eyes with DME after ranibizumab therapy.

Conclusions: Ranibizumab, as administered to patients with DME for 12 to 36 months in these studies, can both improve DR severity and prevent worsening. Prolonged delays in initiation of ranibizumab therapy may limit this therapeutic effect. Although uncommon, the development of PDR still occurs in a small percentage of eyes undergoing anti-vascular endothelial growth factor therapy and may be related to the presence of macular nonperfusion.

Wolf S, et al. 2014.³⁵

RADIANCE: A Randomized Controlled Study of Ranibizumab in Patients with Choroidal Neovascularization Secondary to Pathologic Myopia

Objective: To compare the efficacy and safety of ranibizumab 0.5 mg, guided by visual acuity (VA) stabilization or disease activity criteria, versus verteporfin photodynamic therapy (vPDT) in patients with visual impairment due to myopic choroidal neovascularization (CNV). Design: Phase III, 12-month, randomized, double-masked, multicenter, active-controlled study. Participants: Patients (N = 277) with visual impairment due to myopic CNV. Methods: Patients were randomized to receive ranibizumab on day 1, month 1, and thereafter as needed guided by VA stabilization criteria (group I, n = 106); ranibizumab on day 1 and thereafter as needed guided by disease activity criteria (group II, n = 116); or vPDT on day 1 and disease activity treated with ranibizumab or vPDT at investigators' discretion from month 3 (group III, n = 55). Main Outcome Measures: Mean average best-corrected visual acuity (BCVA) change from baseline to month 1 through months 3 (primary) and 6, mean BCVA change and safety over 12 months. Results: Ranibizumab treatment in groups I and II was superior to vPDT based on mean average BCVA change from baseline to month 1 through month 3 (group I: ≥ 10.5 , group II: ≥ 10.6 vs. group III: ≥ 2.2 Early Treatment Diabetic Retinopathy Study [ETDRS] letters; both P < 0.0001). Ranibizumab treatment guided by disease activity was noninferior to VA stabilization-guided retreatment based on mean average BCVA change from baseline to month 1 through month 6 (group II: ≥ 11.7 vs. group I: ≥ 11.9 ETDRS letters; P < 0.00001). Mean BCVA change from baseline to month 12 was ≥ 13.8 (group I), ≥ 14.4 (group II), and ≥ 9.3 ETDRS letters (group III). At month 12, 63.8% to 65.7% of patients showed resolution of myopic CNV leakage. Patients received a median of 4.0 (group I) and 2.0 (groups II and III) ranibizumab injections over 12 months. No deaths or cases of endophthalmitis and myocardial infarction occurred. Conclusions: Ranibizumab treatment, irrespective of retreatment criteria, provided superior BCVA gains versus vPDT up to month 3. Ranibizumab treatment guided by disease activity criteria was noninferior to VA stabilization criteria up to month 6. Over 12 months, individualized ranibizumab treatment was effective in improving and sustaining BCVA and was generally well tolerated in patients with myopic CNV.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 1, 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 29, 2016

1	exp Bevacizumab/	8913
2	aflibercept.mp.	1014
3	pegaptanib.mp.	594
4	exp Ranibizumab/	2302
5	exp Vascular Endothelial Growth Factors/	43787
6	1 or 2 or 3 or 4 or 5	50503
7	exp Retinal Diseases/	66915
8	exp Macular Degeneration/	16476
9	7 or 8	66915
10	6 and 9	5982
11	limit 10 to yr="2015 -Current"	1075
12	limit 11 to (english language and humans)	946
13	limit 12 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	324

Ocular Vascular Endothelial Growth Factors

Goal(s):

- Promote use of preferred drugs and ensure that non-preferred drugs are used appropriately for OHP-funded conditions.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	Yes: Go to #3	No: Go to #4
3. Will the prescriber consider a change to a preferred product? Message: Preferred products do not require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	Yes: Inform prescriber of covered alternatives in class.	No: Approve for 12 months, or for length of the prescription, whichever is less
4. RPh only: All other indications need to be evaluated as to whether they are funded or contribute to a funded diagnosis on the OHP prioritized list. <ul style="list-style-type: none"> If funded and clinic provides supporting literature: Approve for 12 months, or for length of the prescription, whichever is less. If not funded: Deny; not funded by the OHP. 		

P&T / DUR Review: 3/17 (SS)
Implementation: TBD