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Optical Coherence Tomography Monitoring Strategies for A-VEGF–Treated Age-Related Macular Degeneration: An Evidence-Based Analysis

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Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. The Evidence Development and Standards branch works with expert advisory panels, clinical experts, scientific collaborators, and field evaluation partners to conduct evidence-based reviews that evaluate the effectiveness and cost-effectiveness of health interventions in Ontario.

Based on the evidence provided by Evidence Development and Standards and its partners, the Ontario Health Technology Advisory Committee—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy-makers.

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Abstract

Background

New anti-angiogenesis pharmacotherapies have dramatically altered treatment of age-related macular degeneration (AMD), the leading cause of blindness in older adults. Monthly intraocular injections however, are extremely burdensome to ophthalmologists, patients, and their families. Repeated injections also increase risks of complications or adverse events. Although the pharmacokinetics of anti–vascular endothelial growth factor (A-VEGF) drugs are fairly well known, an individuals' AMD presentation and their pharmacodynamics or response to the drug has been shown to be extremely variable. Therefore treating everyone on the same fixed or standard regimen has potential for undertreating or overtreating patients, and drug costs are not trivial.

Objectives

To review monitoring strategies and to evaluate the role of optical coherence tomography (OCT) in guiding management of A-VEGF–treated neovascular AMD (n-AMD) patients.

Data Sources

Systematic reviews of biographic databases for studies published between 2008 and February 2013 involving A-VEGF–treated n-AMD patients monitored in longitudinal follow-up.

Review Methods

Studies were grouped according to varying treatments, monitoring schedules, and re-treatment protocols reported for n-AMD patients treated with A-VEGF. Several outcomes were evaluated across strategies including visual acuity (VA), retinal anatomy, re-treatment criteria and frequencies of clinical follow-up, OCT imaging investigations, and intravitreal injections. Results were summarized qualitatively, as heterogeneity in study objectives and methods precluded formal meta-analysis.

Results

A systematic review identified 18 randomized controlled trials (RCTs) and 20 observational studies involving A-VEGF treatment employing various monitoring and as-needed (PRN) re-treatment protocols. Several maintenance strategies were unsuccessful, resulting in lower VA gains and stabilization than monthly injections in A-VEGF–treated n-AMD. These included fixed quarterly treatment; fixed quarterly monitoring and PRN re-treatment; and monthly monitoring with either VA-guided re-treatment or quantitative-only VA/OCT- (central retinal thickness [CRT] > 100 μm) guided re-treatment. PRN re-treatment strategies with A-VEGF on the basis of monthly follow-up and rigorous reviews of OCT qualitative and quantitative measures of disease activity did decrease injection burden while maintaining visual gains. Gains in VA obtained with PRN re-treatment in usual clinical practice, however, were not as high as gains in clinical trials.

Conclusions

To reduce treatment burden and provide a more individualized treatment strategy for n-AMD patients, OCT/VA-guided PRN treatment strategies have become the preferred and the dominant maintenance strategy. Success of these strategies, however, is dependent on close monitoring and adherence to tightly defined re-treatment criteria.

Plain Language Summary

Age-related macular degeneration (AMD) is an important retinal disease and the leading cause of irreversible vision loss and blindness in older adults. The emergence of new drugs, targeting anti-vascular endothelial growth factors (A-VEGF), has dramatically altered the treatment of AMD. Optical coherence tomography (OCT) has emerged as a key technology for monitoring treatment of AMD and other retinal disorders.

Although the pharmacokinetics of A-VEGF drugs are fairly well known, patients' AMD presentation and response to the drug can vary greatly. Therefore, treating everyone on the same fixed or standard regimen has potential for under-treating or over-treating patients, and the drug costs are not trivial.

Health Quality Ontario conducted an evidence-based analysis to determine the appropriate monitoring interval with OCT for patients with neovascular AMD (n-AMD) undergoing intraocular injections. The review concluded that for patients with n-AMD, OCT/visual acuity–guided as-needed treatment has become the preferred and dominant maintenance strategy to reduce the treatment burden and increase individualization. Success of these strategies, however, depends on close monitoring and adherence to tightly defined re-treatment criteria.

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List of Abbreviations

AMD	Age-related macular degeneration
ANCHOR	Anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularization in AMD
A-VEGF	Anti-vascular endothelial growth factor
BCVA	Best corrected visual acuity
CATT	Comparison of age-related macular degeneration treatment trials
CI	Confidence interval
CNV	Choroidal neovascularization
CRT	Central retinal thickness
DENALI	Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration
DR	Diabetic retinopathy
EDTRS	Early Treatment Diabetic Retinopathy Study
EVERST	Efficacy and safety of verteporfin PDT in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy
EXCITE	Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration
FA	Fluorescein angiography
FOCUS	RHu FAB V2 ocular treatment combining the use of visudyne to evaluate safety
GA	Geographic atrophy
HORIZON	An extension study to evaluate the safety and tolerability of ranibizumab in subjects with choroidal neovascularization secondary to AMD or macular edema secondary to RVO
IRF	Intraretinal fluid
ITT	Intention-to-treat
IVAN	Alternative treatments to inhibit VEGF in age-related choroidal neovascularization
LCL	Lower confidence limit
MANTRA	A randomized double-masked trial comparing the visual outcome after treatment with ranibizumab or bevacizumab in patients with neovascular age-related macular degeneration
MARINA	Minimally classic/Occult trial of anti-VEGF antibody ranibizumab in the treatment of neovascular AMD
MONT BLANC	Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration
n-AMD	Neovascular age-related macular degeneration

NATTB	Neovascular Age-Related Macular Degeneration Treatment Trial Using Bevacizumab
OCT	Optical coherence tomography
PDT	Photodynamic therapy
PED	Pigment epithelium detachment
PIER	A Phase 111b multicenter randomized double-masked sham injection-controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal choroidal neovascularization (CNV) with or without classic CNV secondary to age-related macular degeneration
PP	Per-protocol
PRN	Pro re nata (as needed)
PrONTO	Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Ranibizumab
RCT	Randomized controlled trial
RF-PDT	Reduced fluence photodynamic therapy
RPE	Retinal pigment epithelium
SAILOR	Ranibizumab in subjects with choroidal neovascularization [CNV] secondary to age-related macular degeneration
SD-OCT	Spectral-domain optical coherence tomography
SECURE	Long-term safety of ranibizumab 0.5 mg in neovascular age-related macular degeneration
SF-PDT	Standard fluence photodynamic therapy
SRF	Subretinal fluid
SUSTAIN	Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration
TD-OCT	Time domain–optical coherence tomography
TTT	Transpupillary thermotherapy
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VIEW	VEGF Trap-EYE investigation of efficacy and safety in wet AMD

Background

Overuse, underuse, and misuse of interventions are important concerns in health care and lead to individuals receiving unnecessary or inappropriate care. In April 2012, under the guidance of the Ontario Health Technology Advisory Committee's Appropriateness Working Group, Health Quality Ontario (HQO) launched its Appropriateness Initiative. The objective of this initiative is to develop a systematic framework for the ongoing identification, prioritization, and assessment of health interventions in Ontario for which there is possible misuse, overuse, or underuse.

For more information on HQO's Appropriateness Initiative, visit our website at www.hqontario.ca.

Age-related macular degeneration (AMD) is an important retinal disease with genetic, aging, and environmental risk factors and is the leading cause of irreversible vision loss and blindness in older adults in the developed world. (1;2) The macula is the part of the retina that enables sharp central vision needed for close work, such as reading and writing, and for driving and recognizing faces.

Vision loss in AMD occurs through 2 distinct mechanisms referred to as dry or wet AMD. Effect of Monthly Ranibizumab on Visual Outcomes in the ANCHOR and MARINA Trials The dry form of AMD accounts for most cases and typically develops before the wet form. Rarely does the wet form (also called exudative or neovascular AMD [n-AMD]) occur without any dry changes or geographic atrophy (GA). Although n-AMD accounts for only 10% to 15% of the overall AMD, it represents more than 80% of the severe visual loss. Effect of Monthly Ranibizumab on Visual Outcomes in the ANCHOR and MARINA Trials In dry or nonexudative AMD, visual loss occurs as a result of GA that is retinal pigment epithelial (RPE) depigmentation of at least 175 µm in diameter or aging-related degeneration and loss of photoreceptors in the foveal centre of the retina. (5) In n-AMD, vision loss is secondary to a neovascularisation or abnormal angiogenesis process. In this process, choroidal capillaries proliferate and penetrate the Bruch membrane reaching the RPE and, in some cases, the subretinal space. These new vessels are more permeable than normal and allow the accumulation of serum and blood under the RPE and/or the neurosensory retina eventually leading to scar formation and irreversible vision loss in an untreated eye.

Vascular endothelial growth factor (VEGF) has a role in both pathologic angiogenesis and normal processes of human growth, development, and tissue repair. Effect of Monthly Ranibizumab on Visual Outcomes in the ANCHOR and MARINA Trials A key factor in this ocular angiogenesis cascade, VEGF produced by the RPE cells leads to a breakdown of the blood-retinal barrier. (5) Several classes of ocular anti-VEGF therapies have been developed because of the detection of VEGF in neovascular membranes, the high incidence of blindness in n-AMD, and our aging population. Effect of Monthly Ranibizumab on Visual Outcomes in the ANCHOR and MARINA Trials Anti-VEGF therapies affect n-AMD disease in several ways: "by inhibiting growth or extension of new vessels; by regressing the neovascularisation; by stabilizing endothelial membranes and reducing permeability of CNV microcirculation; or by reducing diffusion of protein and lipids into extravascular spaces thereby reducing edema and restoring normal central retinal thickness." (5)

There are many classification schemes, grading systems, and severity scales for diagnosis and management of AMD. (7-9) Early stages of AMD are usually asymptomatic and have been characterized in different systems as having drusen and pigmentary alterations within 2 disc diameters of the fovea (or central portion of the macula) that contains specialized cone photoreceptors. (10) Drusen is acellular, polymorphous material that gets deposited between the RPE and Brusch's membrane. (11) A recent

clinical classification scheme derived from expert consensus proposes a 5-stage AMD classification scale. (10) Normal ocular aging without an increased risk of developing late AMD was defined ashaving small drusen or "droplets" ≤ 63 μm and no AMD pigmentary abnormalities. Early AMD stage was defined by the presence of medium-size drusen (≥ 63 – < 125 μm) without AMD-related pigmentary abnormalities. Intermediate AMD stage was defined by the presence of large drusen or pigmentary abnormalities associated with at least medium-size drusen. Those with lesions associated with n-AMD or GA were considered to be late-stage AMD.

The natural history of GA is progressive evolution over several stages with central vision loss increasing gradually over years. (12-14) Vision loss in untreated n-AMD, however, occurs more rapidly than if treated. Complexes formed by the new choroidal vessels can destroy retinal photoreceptors within months. (5) In a meta-analysis of 4,362 treatment-naïve n-AMD patients in 53 study groups (reported before 2006), the proportion of patients developing severe vision loss increased from 10% within 3 months of diagnosis to 20% within 6 months and 43% by 3 years. (15) There is also a 50% chance that n-AMD will become bilateral within 5 years. (5) Depending on the time lag between the initial referral and treatment by retinal specialists, patients with n-AMD could have further visual loss. In a prospective cohort of n-AMD patients referred to an Ontario tertiary care retinal practice, the 28-day median time between referral and treatment was associated with severe vision loss (> 3 lines) in 16%. (16)

In a US population–based cross-sectional survey of patients aged 40 years and older, the estimated prevalence of any (early and late) AMD was 6.5% (95% confidence interval [CI], 5.5–7.6) and the prevalence of late AMD was 0.8% (95% CI, 0.5–1.3). (17) Late AMD was defined as any of the following: GA or RPE detachment, subretinal hemorrhage or visible subretinal new vessels, subretinal fibrous scar, or self- reported history of photodynamic or anti-vascular endothelial growth factor treatment for n-AMD. The prevalence for n-AMD was 0.3% and for pure GA was 0.5%. In the 40- to 59-year age group there were no n-AMD cases, but in the ≥ 60-year age group the prevalence was 0.9%. In a recent meta-analysis of 25 published surveys of AMD prevalence including populations of European ancestry, the prevalence of n-AMD was estimated to increase from 0.04% (95% CI, 0.02–0.07) in 50-year-olds to 2.79% (95% CI,1.99–3.79) in 80-year-olds to 10.49 (95% CI, 7.45–14.37) in 90-year-olds. (18)

Objective of Analysis

The objective of this analysis was to evaluate the monitoring strategies of optical coherence tomography (OCT) for patients with n-AMD under active treatment with anti-angiogenesis pharmacotherapy with A-VEGF. The specific research question was about the appropriate OCT monitoring interval for patients with retinal disease (such as n-AMD) undergoing treatment with A-VEGF pharmacotherapy.

Clinical Need and Target Population

Several retinal disease conditions involve pathways of macular edema and choroidal neovascularization: AMD, diabetic retinopathy (DR), retinal vein occlusion, high myopic choroidal neovascularization, and glaucoma. This review is restricted to evidence on the A-VEGF treatment monitoring strategies for n-AMD, the first indication to gain regulatory approval for A-VEGF pharmacotherapy.

Technology/Technique

A-Vascular Endothelial Growth Factor Pharmacotherapy

The emergence of new anti-angiogenesis pharmacotherapies has dramatically altered the treatment of n-AMD. Two major Phase III regulatory efficacy trials were published in 2006, the MARINA (19) and the ANCHOR, (20;21) each involving ranibizumab (Lucentis®, Genentech) a second-generation biologic anti-VEGF pharmacotherapy for n-AMD patients. The trials, both 2-year 3-arm RCTs with the same key efficacy primary outcomes, involved different comparators. The MARINA was a sham controlled study, and the ANCHOR study involved active controls comparing photodynamic therapy (PDT) with verteporfin (Visudyne®, Novartis), a current therapy for n-AMD. The protocol in both studies involved a 3-month loading dose (3MoLD) of monthly intravitreal ranibizumab injections followed by a maintenance schedule of monthly injections for 24 months.

In both trials, all visual outcome measures were significantly better in the ranibizumab-treated groups (Table 1). Most patients treated with ranibizumab either maintained VA (change over baseline within 15 letters) or increased VA (gain ≥ 15 letters) over baseline. On average the mean gain in best corrected visual acuity (BCVA) evaluated on EDTRS charts at 1-year follow-up over baseline values was 7.2 letters in the MARINA and 11.3 letters in the ANCHOR trials. For the first time, not only was vision stabilized in most patients, but a substantial proportion of patients regained (≥ 15 letters) vision. These trials also had other important results. Visual outcome was shown to decline rapidly over baseline throughout the follow-up in the sham-treated control arm with a BCVA mean loss of 10.4 letters at 1-year follow-up and 14.9 letters at 2-year follow-up. The other major observation was that patients treated with PDT also significantly lost vision over the trial follow-up at a rate similar to that of the sham-treated group.

Table 1. Effect of Monthly Ranibizumab on Visual Outcomes in the ANCHOR and MARINA Trials

Study Treatment	Δ BCVA ETDRS Letters Mean ± SD		Loss < 15 Letters (%)		Gain ≥ 15 Letters (%)		Loss ≥30 Letters (%)	
	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
MARINA (N = 716)								
Sham injection	−10.4	−14.9	62.2	52.9	5.0	3.8	14.3	22.7
0.3 mg of ranibizumab	6.5	5.4	94.5	92.0	24.8	26.1	0.8	3.4
0.5 mg of ranibizumab	7.2	6.6	94.6	90.0	33.8	33.3	1.2	2.5
ANCHOR (N = 423)								
Photodynamic therapy with verteporfin	−9.6 ± 16.4	−9.8 ± 17.6	64.3	65.7	5.6	6.3	13.3	16.1
0.3 mg of ranibizumab	8.5 ± 14.6	8.1 ± 16.2	94.3	90.0	35.7	34.3	0	1.4
0.5 mg of ranibizumab	11.3 ± 14.6	10.7 ± 16.5	96.4	89.9	40.3	41.0	0	0

Abbreviations: BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation.

These trials rapidly established that monthly injections with ranibizumab were the gold standard for n-AMD treatment and has become the standard comparator for regulatory approvals. A modelling study using VA outcomes in these trials estimated that the effect of A-VEGF treatment on the 103,582 United States residents developing n-AMD (for whom ranibizumab was indicated and available) would reduce

the incidence of legal blindness in 2 years by 72% from 16,268 (if untreated) to 4484 cases. (22) Another report evaluated the effect of A-VEGF treatment on blindness in n-AMD patients by comparing the VA outcomes in a cohort of newly diagnosed n-AMD patients treated in a clinical practice in 2002 before the introduction of A-VEGF therapy and in 2008 after its introduction. (23) Forty of the 41 patients of the 2008 cohort received A-VEGF treatment, and the 84 patients in the 2002 cohort were treated with photodynamic therapy, laser photocoagulation, or observation. The prevalence of legal blindness ($VA \leq 20/200$) by 2-year follow-up was significantly ($P = 0.006$) reduced from 29% (95% CI, 19%–39%) in the 2002 cohort to 2% (95% CI, 0–13%) in the 2008 cohort. All other levels of visual impairment were also significantly reduced in the 2008 cohort.

The monthly intravitreal injection treatment regimen, however, is extremely burdensome to ophthalmologists, patients, and their families. The serial repeated intraocular injections also have increased risks of potential complications or adverse events, such as infection, injury, or immune reactions. Although the pharmacokinetics of A-VEGF drugs are fairly well known, (24) an individuals' AMD presentation and their pharmacodynamics or response to the drug has been shown to be extremely variable. Therefore treating everyone with the same fixed regimen has potential for undertreating or overtreating. (25) The drug costs are also not trivial—approximately $1500 per intravitreal injection of ranibizumab. (26)

Given the dramatic responses of patients with n-AMD to ranibizumab A-VEGF therapy in the clinical trials, and because the drug was not available to non-trial participants, there was an interest in another biological A-VEGF agent, bevacizumab (Avastin®, Genentech Inc.), that had regulatory approval but not for n-AMD indications. Bevacizumab had regulatory approval for systemic use in metastatic colorectal cancer but was used off-label for n-AMD. Because of the dose-splitting option of a larger systemic drug volume being applied intraocularly, bevacizumab also had the advantage of lower cost—approximately $40 per intravitreal injection. (26) An analysis of Medicare fee-for-service Part B claims for n-AMD in 2008 that reviewed patterns of use reflected in pharmacologic treatment claims reported bevacizumab was more frequently used than ranibizumab. (26) In the review of the 222,886 AMD patients receiving 1 or more intravitreal injections or infusions, 64.4% (146,276 beneficiaries) received bevacizumab and 35.6% (80,929 beneficiaries) received ranibizumab. A total of 824,525 injections were performed: 480,025 bevacizumab injections for total payments of $20,290,952 and 336,898 ranibizumab injections for total payments of $536,642,693. The national rate per 100,000 beneficiaries was 1,506 for bevacizumab, 1,057 for ranibizumab, 54 for verteporfin, and 24 for pegaptanib sodium (Macugen®, Pfizer) with a significant interstate variation; injection rates were higher for bevacizumab in 39 of 50 states. The substantially higher bevacizumab injection rates suggest that, in practice, bevacizumab is the standard of care for n-AMD.

There is some suggestion that the same pattern of bevacizumab use has evolved in Canada. (23) A review of the Ontario Health Insurance Plan billing claims reported an 8-fold increase in intravitreal drug injections between 2000 and 2007 from 3.5 to 25.9 per 100,000 Ontarians. The median number of monthly injections performed by ophthalmologists also increased significantly from 7.0 in 2005 to 30.5 in 2007. These billing increases in the province predated the approval of ranibizumab (June 2007 by Health Canada and April 25, 2008, by Ontario Drug Branch) by almost a year.

Optical Coherence Tomography

Since the pivotal ANCHOR and MARINA trials, much research has focused on monitoring strategies that involved various flexible-dosing schedules with various re-treatment criteria for treating recurrence in order to decrease injection burden and maintain initial visual gains. (5;25;27;28) Optical coherence tomography (OCT) imaging has increasingly had a key role in these monitoring strategies.

Optical coherence tomography is a non-contact, high-resolution, cross-sectional imaging technique employed in the diagnosis and management of AMD and other retinal disorders. (29-31) Although the role of OCT is still considered complementary to angiography in the diagnosis of AMD, it has become a dominant imaging tool for monitoring disease progression or therapeutic response. (29) The ability to interpret OCT images accurately is becoming a prerequisite for both the retinal specialist and the general ophthalmologist. (30)

The newer generation of OCT devices—spectral-domain OCT (SD-OCT), also known as Fourier-domain or high-resolution OCT—represent technical advances over the earlier time-domain OCT (TD-OCT) devices. (29;30;32) The high speed and greater resolution of SD-OCT devices allows sampling of the macula in greater detail allowing for visualization of retinal anatomy less affected by eye movements. In addition to the automated generation of quantitative measures of clinical significance, such as retinal thickness, OCT also provides qualitative assessments of other anatomic features representing active disease, such as the presence of cystoid spaces, pigment epithelium detachment (PED), or subretinal fluid (SRF) or intraretinal fluid (IRF). (29;30;33) Real-time tracking where the same location can be imaged over time increases the reliability of measurements of change in follow-up exams. (29;30;33) Optical coherence technology continues to advance, and among the new technologies being evaluated for retinal disease management is polarization-sensitive OCT, a technique developed to provide more accurate imaging of the RPE, a key structure in various forms and stages of AMD. (34)

Individualized as-needed re-treatment strategies being developed for monitoring AMD patients treated with A-VEGF therapies are dependent on close monitoring and the reliability and validity of the criteria being used to guide re-treatment decisions. Effective monitoring of disease progression or treatment response depends on accurate and reliable OCT detection and measurement of key retinal anatomic changes representing disease progression. Both quantitative and qualitative OCT measures of retinal change, particularly those associated with choroidal neovascularization (CNV) activity, have been employed to guide treatment. (5;25;27;28) Various quantitative measures of retinal thickness have been employed, such as central retinal thickness (CRT), centre point thickness, retinal volume, and maximum retinal thickness. (35) Various TD-OCT protocols assess quantitative change in retinal thickness, but the fast macular thickness map protocol is preferred because of its rapid image acquisition. (35) Other pathologic anatomic changes associated with n-AMD (such as presence, location, and extent of IRF, SRF, and PED) are also followed longitudinally on OCT and guide treatment decisions.

Both quantitative (33;35-37) and qualitative (33;36;38) OCT retinal measures in n-AMD have been evaluated for reproducibility. Although OCT measurements are based on automatically set threshold algorithms, several variables affect segmentation quality and reproducibility—positioning of segmentation lines, localization control, density of included scan lines, and number of available maps. (39) Reproducibility was shown to be higher for SD-OCT than for TD-OCT devices for all graded qualitative retinal parameters. (38) Several reports (32;39) have also documented significant variation in retinal thickness measurements between SD-OCT devices from different manufacturers. Depending on the devices being compared, clinically significant CRT differences (> 100 μm) were documented, limiting comparisons between OCT devices. (32) Given the significant variation between devices for CRT, it also follows that AMD patients followed longitudinally for disease progression should be evaluated on the same OCT device. Spectral-domain OCT systems were also reported to yield more consensus than TD-OCT on clinical interpretation (presence or absence of IRF or SRF), and in cases of discrepancy, TD-OCT was more likely to detect disease activity than TD-OCT. (38)

Regulatory

After regulatory approval by Health Canada, the Ontario Drug Branch granted approval for ranibizumab in Ontario on April 25, 2008, for use in AMD among those 65 years of age or older and later on November 27, 2012, for use in diabetic macular edema among those 65 years of age or older (personal communication, Ontario Drug Branch June 2013).

Both TD-OCT and SD-OCT devices are licensed by Health Canada as class 11 devices.

Research Question

What is the appropriate monitoring interval with OCT for patients with n-AMD undergoing treatment with A-VEGF pharmacotherapy?

Research Methods

Literature Search

A literature search was performed on February 7, 2013, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2008, until February 7, 2013. The full details of the search are outlined in Appendix 1. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- published between January 1, 2008, and February 7, 2013
- systematic reviews, meta-analyses, health technology assessment reports, randomized controlled trials (RCTs), and controlled trials
- studies evaluating maintenance and follow-up after A-VEGF pharmacotherapy for retinal diseases involving macular edema or choroidal neovascularization
- studies with maintenance or follow-up phases $\geq$ 6 months

Exclusion Criteria

- abstracts
- commentaries, editorials
- studies on OCT used for diagnosis or screening
- studies of pediatric populations

Outcomes of Interest

- monitoring strategies and re-treatment decision criteria
- treatment burden (visits, OCT imaging, and injection frequency)
- anatomic outcomes including retinal thickness
- functional outcomes including visual acuity and contrast sensitivity

Expert Advisory Working Group

In March 2013, an Expert Advisory Working Group on monitoring strategies of OCT for retinal disease was struck. Members of the panel included physicians, personnel from the Ministry of Health and Long-Term Care, and representatives from the Ontario Medical Association. The role of the Expert Advisory Working Group was to contextualize the evidence produced by Health Quality Ontario and provide advice on OCT management of retinal diseases in the province. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the Expert Advisory Working Group.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. (40) The overall quality was determined to be very low, low, moderate, or high using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that RCTs are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas result in downgrading the quality of evidence. Finally, 3 main factors that might raise the quality of evidence were considered: large magnitude of effect, dose-response gradient, and accounting for all residual confounding factors. (40) For more detailed information, please refer to the latest series of GRADE articles. (40)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

Results of Literature Search

The systematic literature search yielded 537 citations published between January 1, 2008, and February 7, 2013 (with duplicates removed). Articles were excluded on the basis of information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

This review was restricted to the studies evaluating patients with n-AMD being treated with A-VEGF pharmacotherapies and being followed up for treatment response or disease progression. Eighteen RCTs and 20 observational studies focusing on patients with n-AMD followed up after treatment with 3 A-VEGF pharmacotherapies (ranibizumab, bevacizumab, and aflibercept [Eylea ®, Regeneron] met the inclusion criteria for this review. The studies included in this review are detailed in Appendix 3.

The studies are grouped and detailed in the following sections according to the various monitoring strategies for A-VEGF treated n-AMD patients that were developed and employed in treatment trials as alternative approaches to the monthly intravitreal injections protocols employed in the MARINA and the ANCHOR trials

Section A. Fixed Quarterly Treatment

Several alternative treatment and monitoring strategies have evolved in order to decrease the treatment burden in n-AMD patients. Less frequent A-VEGF intravitreal injections set at fixed quarterly intervals was one of the first alternative strategies to monthly injections aimed at reducing the treatment burden while maintaining visual gains throughout the maintenance period.

Two large multicentre 3-arm RCTs, the PIER (41;42) and the EXCITE (43) studies, evaluated anatomic and functional outcomes in ranibizumab-treatment that involved fixed quarterly intravitreal injections in a maintenance phase following the initial 3-month loading dose (3-MoLD) of 3 intravitreal ranibizumab injections (Table 2). The PIER trial was sham-controlled, comparing quarterly injections to no treatment, whereas the EXCITE trial directly compared monthly to quarterly injections in the maintenance phase. Optical coherence tomography was used in monitoring for both studies and was performed monthly in the EXCITE trial and 6 times in the first year of the PIER trial.

Table 2: Study Characteristics of Fixed Quarterly Ranibizumab Treatment Trials for n-AMD

Study, Authors, Year, Country	Study Design and Follow-Up	Sites, Patients	Trial Arms	Maintenance Phase and Re-treatment
PIER, Regillo et al, 2008 (42); Abraham et al, 2010 (41); Brown et al, 2013 (44) United States	Multicentre Phase IIIb RCT double-masked, sham injection 2 years	43 sites, 184 Ps Better eye treated and eligible if baseline 20/40 to 20/320 BCVA	3 arms: 0.3 mg ranibizumab, 0.5 mg ranibizumab, sham injection; 3MoLD followed by injections every 3 months	In addition to quarterly injection visits, clinic visits were scheduled at 3, 12, and 24 months. At each visit full ophthalmic assessment included VA testing with ETDRS charts, slit-lamp biomicroscopy, funduscopy, and IOP. Fundus photography and FA were at day 0 and months 3, 5, 8, 12, and 24. OCT was done at day 0 and months 1, 2, 3, 5, 8, 12, and 24
EXCITE, Schmidt-Erfurth et al, 2011 (43) 16 European sites and Australia, Brazil, Israel, and Turkey	Multicentre Phase IIIb RCT double-masked, active controlled Non-inferiority margin 6.8 letters 1 year	59 sites, 353 Ps One eye treated and eligible if BCVA between 73 and 24 letters (~20/40 to 20/320 Snellen equivalent)	3 arms: continuous monthly (0.3 mg ranibizumab) or 3MoLD followed by quarterly injections of 0.3 mg or 0.5 mg of ranibizumab	Monthly VA assessments and TD-OCT exams
NATTB, Liet al, 2012 (45) China	Open-label active control 2-arm superiority RCT 1 year	13 sites, 185 Ps Regimen A: 1.25 mg bevacizumab every 6 weeks for 8 injections Regimen B: 1.25 mg bevacizumab every 6 weeks for first 3 injections (loading dose and injections every 12 weeks)	Before each intravitreal injection, researchers assessed BP and ophthalmic examinations including EDTRS BCVA, IOP, slit-lamp biomicroscopy, fundus examination, FA, and OCT	Initial loading dose of 3 injections at 6-week intervals followed by re-treatment at 6-week or 12-week intervals

Abbreviations: BCVA; best corrected visual acuity; BP, blood pressure; ETDRS; Early Treatment Diabetic Retinopathy Study; FA, fluorescein angiography; IOP, intraocular pressure; 3MoLD, 3-month loading dose; OCT, optical coherence tomography; P, patient; RCT, randomized controlled trial; VA, visual acuity.

In the PIER trial, at 12-month follow-up (42) the sham-treated subjects had lost significantly more best corrected visual acuity (BCVA) over baseline (mean loss 16.3 BCVA ETDRS letters) than either of the different quarterly dosed ranibizumab-treated groups, which had a mean loss of 1.6 BCVA ETDRS letters in the 0.3-mg group ($P = 0.0001$) and a mean loss of 0.2 BCVA ETDRS letters in the 0.5-mg group ($P < 0.0001$). The interval between 3 months and 12 months was the interval representative of the quarterly dosing effect. Over this period there was a mean BCVA loss of 4.5 ETDRS letters for both ranibizumab doses versus a 7.6–ETDRS letter decline in the sham group. At 2-year follow-up, mean BCVA decreased over baseline significantly less ($P < 0.0001$) in both ranibizumab-treated groups (2.2 letters with 0.3 mg and 2.3 letters with 0.5 mg) than the 21.4 letters in the control group. (41) Severe VA loss ($\geq$ 30 letters) affected 33.3% of the controls versus 3% in the ranibizumab-treated groups.

The EXCITE trial was specifically designed to test the non-inferiority (non-inferiority margin of 6.8 letters) of fixed quarterly injections with monthly injections of ranibizumab during the maintenance phase. Both per-protocol (PP) and intention-to-treat (ITT) analyses were performed. The mean gain in BCVA letters was lower in both quarterly dose arms (0.3 mg and 0.5 mg) than in the monthly treatment arms for both the ITT (4.0 ± 14.88 and 2.8 ± 13.78 letters versus 8.0 ± 11.27 letters) and PP (4.9 ± 13.13 and 3.8 ± 13.33 letters versus 8.3 ± 11.31 letters) analyses. Fewer patients improved their BCVA (gaining $\geq$ 15 letters) at 12-month follow-up visits over baseline in the quarterly dosed arms—14.2% in the 0.3-mg group and 17.8% in the 0.5-mg group compared with 28.7% in the monthly dosed arm. Patients' retinal morphology, as shown by OCT-measured CRT was also not well stabilized in the quarterly treated arms. Although the mean reduction over baseline in CRT at 12-month follow-up was similar between the monthly (−105.6 µm) and quarterly dosed arms (−96.0 µm in the 0.3-mg group and −105.3 µm in the 0.5-mg group), the trend over time differed with CRT increasing between quarterly treatment intervals but steadily reducing throughout in the monthly treated group. Non-inferiority of the

quarterly treatment regimen was not achieved, as the lower confidence limits (LCL) were below the non-inferiority threshold of 6.8 letters; the 95% LCL was −7.7 for the 0.3-mg quarterly and −8.6 for the 0.5-mg quarterly ranibizumab arms.

Different dosing and re-treatment strategies with bevacizumab for a Chinese population with n-AMD were evaluated by Li et al (45) in the NATTB study. Visual and anatomic outcomes were compared between various fixed bevacizumab regimens: 1.25 mg every 6 weeks or every 12 weeks after a 3-month loading dose. There were no differences between the arms in VA outcomes at 12-month follow-up. The mean gain in BCVA letters was 12.6 letters in the 6-week and 10.1 letters in the 12-week dosing arm ($P = 0.288$), and there were no differences ($P = 0.602$) between arms in those gaining or losing ≥ 15 BCVA letters. The mean change in OCT-evaluated CRT, however, was greater, but not significantly in the 6-week dosing group (−119 μm vs. −60 μm; $P = 0.221$).

Section B. PRN or As-Needed Maintenance Protocols

Fung et al (46) in the PrONTO study was the first to evaluate an as-needed or PRN re-treatment strategy aimed at tailoring A-VEGF re-treatment to individual recurrence in n-AMD patients. Although the study was a single centre involving only 40 n-AMD patients (mean age 83.5 ± 7.2 years), it provided a detailed time course of treatment responsiveness over 2 years. The study, unlike other studies, included patients with vascular lesions of all types and sizes determined by FA. Follow-up included VA testing and ophthalmoscopic examinations (baseline, days 14, 30, 45, 60, and monthly thereafter); fundus photography and OCT (6 scans) imaging (baseline, days 1, 2, 4, 7, 14, and 30 after the first 2 monthly injections and then monthly), and FA (baseline, months 1, 2, 3, and every 3 months thereafter). Re-treatment criteria, often duplicated in subsequent trials, were strictly defined and included any one of the following 5 occurrences: loss of 5 letters with OCT-detected macular fluid; increase in CRT (distance between inner and outer boundaries) ≥ 100 μm; new-onset hemorrhage, new classic CNV or persistent fluid following the last injection. During the second year, amendments to re-treatment criteria included any qualitative change (retinal cysts, SRF or PED enlargement) on OCT suggestive of recurrent macular fluid.

Of the 880 scheduled study visits during the first 12 months, there was a 99.1% visit compliance. A total of 102 reinjections were performed during months 3 through 12 primarily because of BCVA loss in association with OCT-detected macular fluid. Individual responses were highly variable after the 3-month loading dose—of the 39 eyes that became fluid-free, 7 never needed another injection; 1 eye never became fluid-free and received 13 injections. The mean and median number of consecutive monthly re-injections to achieve a fluid-free macula were 1.2 (± 0.6) and 1 (range, 1–4). After the loading dose the first re-injection was received by 22 patients (67%) patients within the first 6 months and by 11 patients (33%) after 6 months.

The number of exams, injections, and changes over baseline in BCVA and CRT over the 1-year and 2-year PrONTO study period are outlined in Table 3. (46;47) The monthly follow-up with fixed imaging resulted in fewer injections while maintaining the VA levels gained after the loading dose at 1-year follow-up. The significant mean (177.8 μm, $P < 0.001$) and median (185.5 μm, $P < 0.001$) reduction in CRT evaluated by time-domain optical coherence tomography (TD-OCT) paralleled the increase in visual acuity (VA) gains. Significant reductions in CRT over baseline (mean 47 μm, $P < 0.001$) were noted as soon as one day after the first loading injection.

In the second year of follow-up, (47) the BCVA results were maintained with fewer (median 4 vs. 5) injections than the first year. Three eyes received only the first 3 injections (loading dose only) over the 2 years, and 2 eyes required monthly (24 or 25) injections. Vision loss, defined as a loss of 5 letters or more, occurred in 5 patients and was attributable to tears in the RPE (2 eyes), progression of underlying

dry AMD (2 eyes), and formation of subfoveal fibrosis (1 eye). The eyes with vision loss due to underlying dry AMD had an enlargement of GA at a rate of 0.7 disc area per year, which was within a normal expected rate of progression for GA. (13;48)

Table 3: PrONTO Trial Follow-Up in Maintenance Phase

Follow-Up Period, Author, Year	Patients (Eyes)	Visits	Injections Mean ± SD Median (Range)	Δ BCVA Letters Mean ± SD (Median)	Δ CRT µm Mean (Median)
1 year (over baseline) Fung et al, 2007 (46)	40 P (40 E)	Fixed, monthly	5.6 ± 2.3 5.0 (3–13)	9.3 (11)	−178 (−186)
2 years (over baseline) Lalwani et al, 2009 (47)	37 P (37 E)	Fixed, monthly	9.9 ± 5.3 9.0 (3–25)	11.1 ± 12.2 (14)	−212 (−209)

Abbreviations: BCVA; best corrected visual acuity; CRT, central retinal thickness; E, eyes; P, patients; SD, standard deviation.

Variable Loading Phase and PRN Maintenance

The requirement for a loading dose of 3-monthly ranibizumab injections originally used in the ANCHOR and the MARINA trials was uncertain given the variability in response to the loading dose noted in the PrONTO trial. (46) The need for a 3-month loading dose was evaluated by Bolz et al (49) in a prospective survey of 29 consecutive treatment-naïve n-AMD patients treated with ranibizumab. Both retinal anatomic and functional measures showed significant variation in response throughout the 3-month loading-dose phase.

A significant increase in BCVA (5.1 ± 4.0 letters, $P < 0.0001$) over baseline was noted even by week 1 after the first injection, increasing at 3 months to a gain of 6.4 ± 5.8 letters. Increases in absolute changes in central retinal sensitivity were noted at week 1 as well, but changes were highly variable over the loading phase. The anatomic measures on OCT, particularly CRT, showed an immediate and significant decrease of 83 ± 85 µm ($P < 0.0001$) at week 1 that levelled off to 109 ± 98 µm ($P < 0.0001$) at month 3. The number of patients with intraretinal cysts or showing PED rapidly declined by week 1 and slowly leveled off between 1 and 3 months. However, the decrease in PED extension measured by the mean height (286 ± 162 µm to 57 ± 114 µm; $P < 0.010$) and greatest linear diameter (1,918 ± 615 to 466 ± 961 µm; $P < 0.01$) continued to decrease over baseline to the 2-month loading period and then levelled off.

A-VEGF Re-treatment Strategies for n-AMD Evaluated in RCTs

Since the PrONTO trial, various protocols involving as-needed re-treatment strategies during maintenance phases have been employed in various A-VEGF pharmacotherapy RCTs for n-AMD patients. The strategies and their outcomes are grouped and detailed in the following section by the primary objectives of the trials.

PRN Re-treatment Strategies with Ranibizumab or Bevacizumab in RCTs for n-AMD

Two RCTs evaluated the effects of different dosing and re-treatment strategies for A-VEGF treatment of n-AMD—1 study involving ranibizumab (50) and 1 involving bevacizumab. (51) Summaries of the study details are outlined in Table 4.

Table 4: Study Characteristics of PRN Re-treatment Strategies with Ranibizumab or Bevacizumab for n-AMD in RCTs

Study, Author, Year, Country	Study Design and Follow-Up	Sites, Patients, Trial Arms	Maintenance Follow-Up	Re-treatment Criteria
SAILOR, Boyer et al, 2009 (50) United States	Phase III RCT (Cohort 1) and open-label (Cohort 2) 1 year	Cohort 1: 105 sites, 1,169 Ps (0.3 mg), and 1,209 Ps (0.5 mg) Cohort 2: 104 sites, 1,922 Ps RCT Cohort 1: 0.3-mg 3MoLD ranibizumab + PRN vs. 0.5-mg 3MoLD ranibizumab + PRN Cohort 2 with 0.5-mg 1MoLD ranibizumab + PRN	Cohort 1 follow-up visits with OCT, VA ETDRS charts at day 0 and months 3, 6, 9 and 12 Cohort 2 follow-up visits with VA at day 0 and months 6 and 12	Cohort 1 based on 1) BCVA ETDRS letter decrease > 5 compared with highest at any prior visit 2) VA as above or OCT > 100 µm CRT, with IRF or SRF Cohort 2 Re-treatment was at physician's discretion
El-Mollayess et al, 2012 (51) Lebanon and France	Open-label single masked RCT	2 sites, 120 Ps Randomized after a loading dose of 2 monthly injections to either continued fixed dosing every 4–6 weeks or variable dosing 1.25 mg of bevacizumab	At follow-up: slit-lamp examination, dilated fundus examination, and monthly OCT and BCVA	1) Recurrence or presence of any fluid in the macula on OCT 2) CRT increased ≥ 50 µm from lowest value 3) VA loss ≥ 5 letters with OCT evidence of fluid in the macula 4) New macular hemorrhage 5) New area of classic CNV amendment addition 6) appearance of new PED, or increased size in previously stable PED

Abbreviations: BCVA, best corrected visual acuity; CNV, choroid neovascularisation; CRT, central retinal thickness; ETDRS; Early Treatment Diabetic Retinopathy Study; IRF, intraretinal fluid; 1MoLD, 1-month loading dose; 3MoLD, 3-month loading dose; n-AMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; P, patient; PED, pigment epithelium detachment; PRN, pro re nata (as needed); RCT, randomized controlled trial; SRF, subretinal fluid; VA, visual acuity.

The SAILOR study (50), a large multicentre Phase III RCT, investigated the effects of two different doses (0.3 mg vs. 0.5 mg) of ranibizumab for previously treated or treatment-naïve n-AMD patients using a standard 3-month loading dose followed by fixed visits and as-needed or PRN re-treatment in 12-month follow-up. In this study, PRN re-treatment was based on defined BCVA and OCT criteria with fixed visit schedules in the maintenance phase, followed by quarterly visits for the differently randomized dosed ranibizumab study arms in Cohort 1, and with visits every 6 months in Cohort 2.

Investigating physicians used the BCVA and OCT re-treatment criteria for 81% of the patients in either ranibizumab-dosed group in Cohort 1. The average number of visits was 8.8 and of injections was 4.4 in the 12-month follow-up. The scheduled number of visits was 7; between the scheduled visits, approximately 40% of the patients made unscheduled visits at each interval month. The mean visual gains over baseline BCVA after the loading dose phase for any of the study groups were not as high as they were in the earlier MARINA or ANCHOR studies, and even these gains steadily declined over the maintenance period with this PRN re-treatment but fixed monitoring schedule (Table 5). The proportion of patients gaining BCVA (≥ 15 letters) after the loading phase, however, did remain stable over the maintenance phase. Retinal thickness OCT measures improved (decreased) after the loading phase and also steadily worsened (increased) in the maintenance period.

Table 5: Fixed Quarterly Visits and PRN A-VEGF Re-treatment on Outcomes in RCTs for n-AMD

Study Group	Δ ETDRS BCVA Letters Mean		Proportion (%) Gaining ≥ 15 Letters		Δ CRT µm Mean	
	0–3 months	0– 2 months	0–3 months	0–12 months	0–3 months	0–12 months
Treatment naïve, 0.3 mg	5.8	0.5	19.4	14.6	−107.0	−72.0
Treatment naïve, 0.5 mg	7.0	2.3	20.1	19.3	−122.0	−92.0
Previously treated, 0.3 mg	4.6	1.7	16.0	15.8	−98.0	−71.0
Previously treated, 0.5 mg	5.8	2.3	18.6	16.5	−108.0	−76.0

Source: Boyer et al. (50)

Abbreviations: BCVA; Best corrected visual acuity; CRT, Central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; n-AMD, neovascular age-related macular degeneration; PRN, pro re nata (as needed).

The El-Mollayees et al (51) study directly compared a monthly treatment regimen to a variable OCT-guided re-treatment protocol. At 12-month follow-up, the number of injections was significantly reduced in the OCT-guided PRN re-treatment arm compared with the fixed re-treatment arm (3.8 vs. 9.5 injections; $P < 0.001$) without affecting VA gains. The mean gain in BCVA over baseline was higher but not significantly different ($P = 0.37$) between the fixed treated arm and the OCT-guided PRN-treated arm: 11.0-letter gain versus 9.2-letter gain, respectively. The vision outcomes were also consistent with changes in OCT-measured retinal anatomic outcomes. The mean decrease in CRT over baseline was not significantly different in the 2 arms: 261.2 µm (range −100.5 µm to −268.9 µm) in the OCT-guided group and 268.87 µm (range 80.7–261.2 µm) in the fixed-treatment arm.

PRN Re-treatment Strategies for n-AMD and Effect of Combination A-VEGF and Photodynamic Intervention RCTs

Verteporfin photodynamic therapy (PDT) and A-VEGF therapies target different processes in n-AMD. Joint use was believed to possibly have a synergistic effect achieving greater or more durable vision benefits and reducing the number of overall treatments. (52) Six trials (52-57) investigated the effects of PRN re-treatment strategies (all except 1 trial (58) involved OCT criteria) on treatment burden: either visits or injections over the maintenance phase within treatment trials evaluating combined A-VEGF and PDT effects, either standard fluence (SF-PDT) or reduced fluence (RF-PDT) on n-AMD. One of the studies (56) involved a different laser approach, transpupillary thermotherapy (TTT), which is intended to induce vascular occlusion with a longer radiation wavelength than PTD (810 vs. 689 nm) and is delivered through the pupil to the target tissue. The details of the studies are outlined below in Table 6.

Three of these clinical trials—DENALI, (52) MONT BLANC, (54) and EVERST (58)—were part of the SUMMIT international clinical trial program designed to evaluate the relative therapeutic benefits of a joint intervention of PDT and A-VEGF compared with ranibizumab or PDT monotherapy. The studies were conducted in various regions (DENALI in United States and Canada, MONT BLANC in Europe, and EVERST in Asia) with the DENALI and the MONT BLANC trials focusing on subfoveal CNV secondary to AMD. The EVERST trial differed from the other 2 by focusing on polpoidal choroidal vasculopathy, presumed to be a subtype of n-AMD where lesions originate from the inner choroidal vasculature (58) The condition is more common in Asian and African-American populations (59) and is associated with high rates of hemorrhage and recurrent leakage. A combined PDT and A-VEGF treatment for this condition is thought not only to stabilize vision, resolve hemorrhage, and decrease macular edema, but also to more effectively treat polyp regression. However, as the EVERST trial also differed from the others in that it was primarily an indocyanine green angiography-guided study with polyp regression as the primary outcome, the results were not comparable with the other studies.

Table 6: Study Characteristics of PRN Re-treatment with Combination A-VEGF and Photodynamic Intervention Trials for n-AMD

Study, Author, Year, Country	Study Design and Follow-Up	Sites, Patients, Trial Arms	Maintenance Follow-Up	Re-treatment
DENALI, Kaiser et al, 2012 (52) United States and Canada	3-arm double-masked sham-controlled multicentre Phase III non-inferiority RCT 1 year	Various sites, 321 Ps Verteporfin half-fluence PDT+ 0.5 mg 3MoLD + PRN ranibizumab vs. verteporfin standard fluence PDT + 0.5 mg 3MoLD ranibizumab + PRN vs. sham verteporfin PDT + 0.5 mg 3MoLD ranibizumab followed by monthly injections	Monthly visits included OCT, ophthalmic examination, VA assessment. FA was performed as needed	OCT-defined criteria including 1) SRF or 2) cystoid macular edema or 3) increased PED > 100 µm or 4) retinal thickness increased by 100 µm over the best prior value. Also if new hemorrhage developed or VA decreased by ≥ 5 letters and if FA indicated CNV leakage
Krebs et al, 2013 (53) Austria	2-arm single-masked RCT 1 year	3 sites, 51 Ps 3MoLD ranibizumab + PRN vs. combined therapy 3MoLD ranibizumab and next-day standard fluence PDT + PRN	Monthly examinations including biomicroscopy of the anterior and posterior segment, VA, OCT, IOP, and evaluation of adverse events. FA at baseline and at 12 months	Signs of lesion activity in OCT, FA, or biomicroscopy
MONT BLANC, Larsen et al, 2012 (54) 12 European countries	2-arm double-masked non-inferiority RCT 1 year	45 sites, 255 Ps Verteporfin standard fluence PDT + 0.5-mg 3MoLD ranibizumab + PRN vs. sham verteporfin PDT + 0.5-mg 3MoLD ranibizumab + PRN	Monthly visits included VA and OCT. Digital FA and colour fundus photography were performed at screening, months 3 and 12, and month between on basis of re-treatment criteria	Functional and anatomic criteria included 1) ≥ 100-µm CRT (from lowest previous) 2) presence of SRF or hemorrhage 3) BCVA decrease > 5 letters 4) or leakage on FA
Rudnisky et al, 2010 (55) Alberta Canada	Retrospective parallel cohorts 1 year	Group retinal practice, 347 Ps Group 1: 1.25 mg bevacizumab vs Group 2: same-day 1.25 mg bevacizumab and half-fluence PDT. Assignment at retinal specialist's discretion	Visits at approximately 3-month intervals including OCT	Presence of SRF or IRF on clinical exam or on OCT or if VA was reduced from VA at prior visit
Soderberg et al, 2012 (56) Sweden	2-arm double-masked sham-controlled RCT 2 year	1 site, 100 Ps ranibizumab + sham TTT + PRN ranibizumab vs. ranibizumab 1MoLD + fixed quarterly TTT and PRN ranibizumab	Monthly visits included ETDRS BCVA, slit-lamp biomicroscopy, IOP, OCT, and FA at 12 and 24 months	Re-treatment on basis of any of the following: 1) loss of ≥ 5 BCVA ETDRS letters 2) increase OCT CRT ≥ 100 µm 3) new classic CNV 4) new submacular hemorrhage 5) persistent IRF or SRF
Williams et al, 2012 (57) United States	2-arm unmasked RCT 1 year	Multicentre, 60 Ps ranibizumab 3MoLD + PRN vs. PDT and 1MoLD ranibizumab + PRN	Monitored monthly	Based on clinical discretion using ETDRS BCVA, clinical findings, and OCT

Abbreviations: BCVA, best corrected visual acuity; CNV, choroidal neovascularization; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fluorescein angiography; IOP, intraocular pressure; IRF, intraretinal fluid; 1MoLD, 1-month loading dose; 3MoLD, 3-month loading dose; OCT, optical coherence tomography; P, patient; PDT, photodynamic therapy; PED, pigment epithelium detachment; PRN, pro re nata (as needed); RCT, randomized controlled trial; SRF, subretinal fluid; TTT, transpupillary thermotherapy; VA, visual acuity.

The SUMMIT clinical trials, DENALI and MONT BLANC, were both designed as non-inferiority trials with similar protocols. In both trials OCT and VA criteria were used to guide re-treatment, although the protocol in the DENALI study was much more stringent than that in the MONT BLANC trial, which allowed for investigator discretion with the defined re-treatment criteria. In both studies, visual outcomes were better in the monotherapy ranibizumab-treated arm than in the joint treated arm at 1-year follow-up:

mean VA was higher, more patients gained clinically significant vision, and fewer lost clinically significant vision (Table 7). The greatest difference between the study groups was the percentage of patients gaining VA, which ranged from 41.1% in the monthly ranibizumab-treated arm to 18.2% in the MONT BLANC SF-PDT–treated arm.

In the DENALI study, ranibizumab monotherapy was monthly and joint therapy group ranibizumab was PRN with monthly visits. Although the mean number of reinjections was reduced in both the RF-PDT (5.7 reinjections) and the SF-PDT (5.1 reinjections) groups, neither group demonstrated non-inferiority (7-letter margin) of VA to ranibizumab montherapy. The lower confidence limits (97.5% LCL) for mean VA gains at 1-year follow-up were −7.90 for the SF-PDT group and −8.51for the RF-PDT group.

In the MONT BLANC study, maintenance re-treatment protocol was PRN, and the mean VA gains at 1 year were not as high as those in the DENALI study. Noninferiority defined as a 7-letter margin, of the jointly treated group was shown to the PRN monotherapy ranibizumab-treated group (95% CLL, −5.76). However, differences between the study arms in the mean number of re-treatments, or the proportion of patients having injection-free intervals of 3 months or greater were not significant in either trial. Improvements in retinal anatomic measures (CRT) paralleled visual changes in that the greatest improvements occurred in the monthly treated ranibizumab monotherapy arm.

The 4 other smaller studies (53;55-57) contributed similar information on comparisons between ranibizumab and combination ranibizumab and laser treatment (Table 7). Visual acuity gains were higher in the ranibizumab or bevacizumab monotherapy arms than in the jointly treated arms with either PDT or TTT laser interventions. In the Soderburgh et al (56) trial, in which patients were followed for 2 years, the mean number of injections was lower (8.0 in PRN ranibizumab and TTT and 6.3 in PRN ranibizumab) than the mean number of re-treatments in the 12-month follow-up of the monthly treated (10.6) ranibizumab group.

Table 7: Outcomes of PRN Re-treatment and A-VEGF and Photodynamic Combination Intervention Trials

Study Arm	Δ ETDRS BCVA Letters Mean ± SD	Proportion (%) Gaining ≥ 15 Letters	Proportion (%) Losing ≥ 15 Letters	Δ CRT Mean (μm)	Injections Mean ± SD (Interval)	Proportion Injection Free-Interval ≥ 3 Months (95% CI)
DENALI (52)						
Sham PDT + 0.5 mg of ranibizumab monthly	8.1 ± 15.1	41.1	8.4	−172.2 ± 166.7	7.6 (months 3–11)	NA
SF-PDT + 0.5-mg 3MoLD of ranibizumab and PRN	5.3 ± 15.7	31.3	8.4	−151.7 ± 135.6	2.2 (months 3–11)	92.6% (85.4–97.0)
RF-PDT + 0.5-mg 3MoLD of ranibizumab and PRN	4.4 ± 15.5	24.7	11.8	−140.9 ± 135.6	2.8 (months 3–11)	83.5% (74.6–90.3)
MONT BLANC (54)						
Sham PDT + 0.5-mg 3MoLD of ranibizumab and PRN	4.4 ± 15.9	25.8	9.1	−107.7 ± 11.02	2.2 (months 3–11)	92%
SF-PDT + 0.5-mg 3MoLD of ranibizumab and PRN	2.5 ± 14.8	18.2	13.2	−115.3 ± 9.04	1.9 (months 3–11)	96%

Study Arm	Δ ETDRS BCVA Letters Mean ± SD	Proportion (%) Gaining ≥ 15 Letters	Proportion (%) Losing ≥ 15 Letters	Δ CRT Mean (μm)	Injections Mean ± SD (Interval)	Proportion Injection Free-Interval ≥ 3 Months (95% CI)
Williams et al (57)						
0.5-mg 3MoLD of ranibizumab and PRN	9.9 ± 23.9	33	22	−92.5 ± 111.26	3.8 (9 months)	--
RF-PDT + 0.5-mg 1MoLD of ranibizumab and PRN	2.6 ± 18.5	14	31	−106.7 ± 94.12	2.0 (11 months)	--
Krebs et al (53)						
0.5-mg 3MoLD ranibizumab and PRN	5.1	NR	9.1	−81.49	6.3	--
PDT + 3MoLD of ranibizumab and PRN	−7.1	NR	31.6	−138.2	4.7	--
Rudnisky et al (55)						
1.25-mg 1MoLD of bevacizumab	5.1	33.8	25.9	NR	3.32 ± 1.71 (R, 1–8) (0–12 months)	--
RF-PDT + 1.25-mg 1MoLD of bevacizumab	4.8	39.0	19.9	NR	3.14 ± 1.52 (R,1–7) (0–12 months)	--
Soderburgh et al (56)						
0.5-mg 3MoLD of ranibizumab + sham	4.0 ± 1.8	7.5	NR	−166	8.0 ± 3.3 (0–24 months)	--
0.5-mg 3MoLD of ranibizumab + TTT	1.0 ± 2.8	18.4	NR	−121	6.3 ± 2.8 (0–24 months)	--

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; 1MoLD, 1-month loading dose; 3MoLD, 3-month loading dose; NA, not applicable; PDT, photodynamic therapy; PRN, pro re nata (as needed); RF-PDT, reduced fluence photodynamic therapy; SD, standard deviation; SF-PDT, standard fluence photodynamic therapy; TTT, transpupillary thermotherapy.

PRN Re-treatment Strategies for n-AMD in Comparative A-VEGF RCTs with Ranibizumab Versus Bevacizumab

Four RCTs (60-63) compared ranibizumab and bevacizumab A-VEGF treatment of n-AMD; 3 (60-62) were large multicentre Phase III RCT s. The other RCT (63) was conducted with a specialized patient study group of American veterans and was much smaller than the others. These studies are summarized in Table 8.

The Phase III trials were all designed as non-inferiority trials (bevacizumab not inferior to ranibizumab) with similar non-inferiority margins—5 letters for the CATT trial (62), 3.5 letters for the IVAN trial (60), and 7.0 letters for the MANTRA trial (61). The trials involved either a 1- or 3-month drug loading followed by a monthly or an as-needed re-treatment maintenance period. In all trials, OCT criteria along with worsening VA were major protocol-defined criteria for re-treatment. In the IVAN trial, the re-treatment protocol indicated further injections every 3 months rather than 1 injection in the presence of active disease.

Table 8: Study Characteristics of Ranibizumab Versus Bevacizumab A-VEGF RCTs for n-AMD

Study, Author, Year, Country	Study Design and Follow-Up	Sites, Patients, Trial Arms	Maintenance Follow-Up	Re-treatment Criteria
CATT, Catt Research Group, 2011, (62;64;65) United States	4-arm active groups, single-masked multicentre non-inferiority RCT 1–2 years	44 sites, 1208 Ps 1MoLD of ranibizumab + M 1MoLD of ranibizumab + PRN 1MoLD of bevacizumab + M 1MoLD of bevacizumab + PRN	Follow-up included: monthly ophthalmologic exams; TD-OCT (PRN only), VA, and FA performed at the investigators' discretion	1) Fluid on TD-OCT 2)) new or persistent hemorrhage 3) decreased VA (before previous) 4) dye leakage or FA showing increased lesion size
MANTRA, Krebs et al, 2013, (61) Austria	2-arm active groups double-masked multicentre non-inferiority RCT 1 year	10 sites, 321 Ps 3MoLD of ranibizumab + PRN 3MoLD of bevacizumab + PRN	Follow-up included monthly study visits with biomicroscopy, IOP, BCVA, OCT, medicine and adverse event check; FA was performed at baseline and at 12 months	1) VA decreased ≥ 5 letters with OCT or FA evidence of macular fluid 2) CRT increased ≥ 100 µm on OCT 3) new macular hemorrhage 4) new area showing CNV 5) persistent fluid on OCT(> 1month after injection)
IVAN, Chakravarthy et al, 2012, (60) United Kingdom	4-arm active groups single-masked multicentre non-inferiority RCT 1 year	23 sites, 628 Ps 3MoLD of ranibizumab + BiM 3MoLD of ranibizumab + PRN 3MoLD of bevacizumab + BiM 3MoLD of **b**evacizumab + PRN	Follow-up included monthly visits with BCVA, clinical exams, OCT, and fundus photography with FA at baseline and months 12 and 24	1) On OCT any SRF, increasing IRF, or fresh blood 2) VA decrease by ≥ 10 letters 3) On FA leakage > 25% lesion circumference or expansion CNV
Subramanian et al, 2012, (63) United States	2-arm active groups double-masked RCT 1 year	1 site, 28 Ps (Veterans Affairs) 3MoLD of ranibizumab + PRN 3MoLD of bevacizumab + PRN	Follow-up included monthly visits with VA, OCT, and clinical exams	1) On OCT any qualitative increase in IRF or SRF 2) Worsening VA 3) Increased fluid or hemorrhage leading to FA

Abbreviations: BCVA, best corrected visual acuity; BiM, bimonthly; CNV; classic neovascularization; CRT, central retinal thickness; FA; fluorescein angiography; IOP, intraocular pressure; IRF, intraretinal fluid; 1MoLD, 1-month loading dose; 3MoLD, 3-month loading dose; M, monthly; OCT, optical coherence tomography; P, patient; PRN, pro re nata (as needed); SRF, subretinal fluid; RCT, randomized controlled trial; TD-OCT, time domain–optical coherence tomography; VA, visual acuity.

The visual and anatomic outcomes of the various dosing and re-treatment strategies at 1-year follow-up in the 4 comparative A-VEGF treatment trials are outlined in Table 9. The pairwise comparisons of inferiority in the CATT trial are outlined in Table 10.

Table 9: Outcomes of Ranibizumab Versus Bevacizumab Re-Treatment Strategies for n-AMD in RCTs

Study Group	Δ ETDRS BCVA Letters Mean ± SD 1 Year (2 Years)	Proportion (%) Gaining ≥ 15 BCVA Letters over 1 Year	Proportion (%) Losing ≥ 15 BCVA Letters over 1 Year	Δ CRT µm Mean ± SD 1 Year	Visits and OCT Exams	Injections Mean ± SD 1 Year (2 Years)
CATT (N = 1,208)						
Ranibizumab monthly	8.5 ± 0.8 (8.8 ± 15.9)	34.2	5.6	−196 ± 176	Fixed	11.7 ± 1.5 (22.4 ± 3.9)
Ranibizumab PRN	6.8 ± 0.8 (6.7 ± 4.6)	24.9	4.6	−168 ± 186	Fixed	6.9 ± 3.0 (12.6 ± 6.6)
Bevacizumab monthly	8.0 ± 1.0 (7.8 ± 15.5)	31.3	6.0	−164 ± 181	Fixed	11.9 ± 1.2 (23.4 ± 2.8)
Bevacizumab PRN	5.9 ± 1.0 (5.0 ± 17.9)	28.0	8.0	−152 ± 178	Fixed	7.7 ± 3.5 (14.1 ± 7.0)
MANTRA (N = 321)						
Ranibizumab PRN	4.9	NR	NR	−89.9	Fixed	5.8 ± 2.7
Bevacizumab PRN	4.1	NR	NR	−86.3	Fixed	6.1 ± 2.8
IVAN (N = 628)						
Ranibizumab (monthly + PRN)	6.4 ± 12.8	23.0	5.0	−155 ± 182	Fixed	10.0 (IQR 6,12)
Bevacizumab (monthly + PRN)	4.7 ± 12.5	16.0	4.0	−139 ± 182	Fixed	11.0 (IQR 7,12)
Monthly (ranibizumab + bevacizumab)	6.1 ± 14.1	20.0	5.0	−168 ± 189	Fixed	12.0 (IQR 11,12)
PRN (ranibizumab + bevacizumab)	5.0 ± 11.1	19.0	4.0	−127 ± 174	Fixed	7.0 (IQR 6,9)
Subrananian (N = 28)						
Ranibizumab PRN	6.3	14.3	14.3	−91	Fixed	4 (R, 3–6)
Bevacizumab PRN	7.6	33.3	0	−50	Fixed	8 (R, 3–12)

Abbreviations: BCVA, best corrected visual acuity; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; IQR, interquartile range; NR, not reported; OCT, optical coherence tomography; PRN, pro re nata (as needed); R, range; SD, standard deviation.

The CATT trial (62) evaluated the differences of a monthly or a PRN re-treatment strategy for both ranibizumab and bevacizumab at 1-year follow-up and in the second year (64) evaluated the effects of switching from a monthly to a PRN re-treatment strategy. In the first year the mean BCVA improved by 7 letters and did not differ among the treatment groups ($P = 0.16$). There were no differences in any of the visual outcomes (proportion losing or gaining letters) between the study drug groups within the same re-treatment protocol. The mean gain in BCVA letters was lower, but not significantly ($P = 0.16$) in both PRN treatment groups compared with monthly treatments.

The pairwise comparisons of non-inferiority are summarized in Table 10. Bevacizumab was not inferior to ranibizumab for BCVA outcome (within the 5-letter non-inferiority limit) when given monthly (99.2% LCL, −3.9 letters) and when given PRN (99.2% LCL, −4.1 letters). However, within drugs, PRN re-treatment was inferior to monthly. Both drugs also resulted in significant reductions in CRT ($P = 0.03$), although reductions ranged from −152 ± 178 with bevacizumab PRN to −196 ± 176 with ranibizumab monthly. There was, however, a significant ($P < 0.001$) and similar reduction ($P < 0.001$) in the number of

re-treatments in the PRN (vs. monthly) in both the bevacizumab (7.7 ± 3.5 vs. 11.9 ± 1.2) and ranibizumab (6.9 ± 3.0 vs. 11.7 ± 1.5) groups.

Table 10: CATT Non-Inferiority RCT Comparisons of Bevacizumab Versus Ranibizumab for n-AMD

CATT Comparison at Year 1				
Group 1	**Group 2**	**Δ ETDRS BCVA Letters Mean**	**99.2% CI**	**Inferiority Comparison**
Bevacizumab monthly	Ranibizumab monthly	−0.5	−3.9 to 2.9	Not inferior
Bevacizumab PRN	Ranibizumab PRN	−0.8	−4.1 to 2.4	Not inferior
Ranibizumab PRN	Ranibizumab monthly	−1.7	−4.7 to 1.3	Not inferior
Bevacizumab PRN	Bevacizumab monthly	−2.1	−5.7 to 1.6	Inferior
Ranibizumab PRN	Bevacizumab monthly	−1.2	−4.5 to 2.1	Not inferior
Bevacizumab PRN	Ranibizumab monthly	−2.6	−5.9 to 0.8	Inferior

Abbreviations: BCVA, best corrected visual acuity; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, pro re nata (as needed).

In the second year, there was little change from the first year in the mean BCVA in the study groups. The difference in mean BCVA improvement between patients treated with bevacizumab relative to ranibizumab was −1.4 letters (95% CI, −3.7 to 0.8) and between those treated by a PRN regimen relative to monthly treatment was −2.4 letters (95% CI, −4.8 to −0.1). The rate of GA (mainly non-foveal), in those not having it at baseline, was significantly higher in the ranibizumab monthly treatment group than in the bevacizumab PRN treatment group (25.8% vs. 12.9%, $P = 0.007$).

Patients in the monthly treatment groups were randomly switched in the second year to the PRN re-treatment protocol to evaluate the effect of switching. At the 2-year follow-up, patients in both drug groups in the monthly regimen experienced little change in mean BCVA at 2-year follow-up. The ranibizumab monthly treatment group continuing in the monthly treatment group lost 0.3 ± 11.1 letters over the first year, and the bevacizumab monthly treatment group lost 0.6 ± 10.3 letters. However, patients in both drug groups switched to PRN re-treatment had a greater mean BCVA loss: 1.8 ± 11.2 letters in the ranibizumab-switched group and 3.6 ± 12.1 letters in the bevacizumab-switched group. As with the other PRN-treated groups, the number of injections in the second year was significantly reduced in the switched PRN group compared with the continued monthly groups for both ranibizumab (5.0 ± 3.8 vs. 10.5 ± 3.1) and bevacizumab (5.8 ± 4.4 vs. 11.3 ± 2.3). Overall at 2-year follow-up, 60% or more of patients in all groups had vision 20/40 or better.

In the MANTRA trial, VA increased significantly in both bevacizumab and ranibizumab groups re-treated on a PRN protocol at 1-year follow-up (Table 9). The difference in mean BCVA gain over baseline between drugs (bevacizumab minus ranibizumab) of −1.99 letters (95% CI, −4.04 to 0.06) was within the non-inferiority margin. The between re-treatment strategies (PRN minus monthly) was −0.35 (95% CI, −2.40 to 1.70). The CRT decreased significantly in both drug groups, and between-group difference were not significant ($P = 0.81$). The PRN re-treatment schedule also resulted in similar number of reduced reinjections (compared with monthly) for both drug groups.

The results in the IVAN trial were not presented separately for drug type (ranibizumab or bevacizumab) or for re-treatment strategy (monthly or PRN)—outcomes were pooled across drug type or reintervention strategy (Table 9). The difference between drug groups (bevacizumab minus ranibizumab) pooled by re-intervention strategy in the primary outcome of the mean gain in BCVA at 1-year follow-up was −1.99 letters (95% CI, −4.04 to 0.06) below the 3.5 non-inferiority threshold. The difference between the re-treatment regimens (PRN minus monthly) pooled by drug type at −0.35 (95% CI, −2.40 to 1.70) was not below the non-inferiority threshold. The PRN re-treatment regimen in this trial also resulted in fewer re-treatments—7 versus 12 reinjections.

The Subramanian et al (63) study was a small RCT using an OCT-guided re-treatment strategy and comparing VA outcomes in n-AMD treatment-naïve veterans treated with A-VEGF therapies in a tertiary care referral centre for veterans in New England. Visual acuity was improved in both drug treatment groups at 1-year follow-up and the difference (ranibizumab minus bevacizumab) in mean BCVA gain was not different between the 2 groups (1.3 ± 14.9 letters; 95% CI, 0.64–15.5). The mean change in CRT over baseline between the groups at follow-up was also not significantly different (77.5 ± 151; $P = 0.29$). The number of reinjections in the ranibizumab-treated group was significantly fewer than in the bevacizumab group (4.0 vs. 8.0, $P = 0.001$).

Re-treatment Strategies in Aflibercept Versus Ranibizumab RCTs for n-AMD

Aflibercept is a new class of A-VEGF drug with stronger binding affinity to VEGF than ranibizumab (66;67) was evaluated for effectiveness and improvement over the need for either monthly injections or monitoring visits.

Two large Phase III RCTs designed in parallel, the VIEW 1 conducted in the United States and Canada and the VIEW 2 conducted in Europe, Asia, and Australia, compared the efficacy of aflibercept and ranibizumab for n-AMD (Table 11). (68) The primary endpoint for the trials was non-inferiority of intravitreal aflibercept to ranibizumab in the proportion of patients maintaining vision (losing < 15 ETDRS BCVA letters in PP analysis) at 1-year follow-up. In both trials, after 3MoLDs, drugs were injected at various doses either monthly or bimonthly. The regulatory agencies for the trials requested differing non-inferiority margins. The FDA used a 10% non-inferiority margin, and the European Medicines Agency/Committee for Medicinal Products for Human used a 7% non-inferiority margin and a 5% margin for assessing clinical equivalence.

Table 11: Study Characteristics of Ranibizumab Versus Aflibercept RCTs for n-AMD

Study, Author, Year, Country	Study Design and Follow-Up	Sites, Patients (P)	Trial Arms	Follow-Up Investigations
VIEW 1, Heir et al, 2012, (68) United States and Canada	4-arm, double-masked multinational, parallel-group active control non-inferiority RCT 1 year	154 sites, 1,217 Ps	Randomization to monthly 0.5 mg of aflibercept, monthly 2.0 mg of aflibercept, or 2 mg of aflibercept every 2 months or 0.5 mg of ranibizumab monthly	Monthly visits including VA, anterior/posterior exam with IOP. Fundus photography and FA at baseline and at weeks 24 and 52, and OCT at baseline and at weeks 4, 12, 24, 36, and 52 and optional between scheduled dates
VIEW 2, Heir et al, 2012, (68) Europe, Middle East, Asia-Pacific, and Latin America	4-arm, double-masked multinational, parallel-group active control non-inferiority RCT 1 year	172 sites, 1,240 Ps	Randomization to monthly 0.5 mg of aflibercept, monthly 2.0 mg of aflibercept or 2 mg of aflibercept every 2 months, or 0.5 mg of ranibizumab monthly	Monthly visits including VA, anterior/posterior exam with IOP. fundus photography and FA at baseline, weeks 24 and 52, and OCT at baseline and weekly afterward

Abbreviations: FA, fluorescein angiography; IOP, intraocular pressure; OCT, optical coherence tomography; P, Patient; RCT, randomized controlled trial; VA, visual acuity.

All of the aflibercept dosing groups in both the VIEW 1 and VIEW 2 trials and the integrated analysis achieved statistical non-inferiority for the primary outcome of maintaining vision (proportion losing < 15 ETDRS letters) at 1 year compared with monthly ranibizumab. The confidence interval of the difference between ranibizumab and aflibercept was within the prescribed 10% and 7% non-inferiority lower limits, and also within the prescribed 5% margin for clinical equivalence. The proportion of patients with VA-stabilized (loss of < 15 letters) was greater than 90% in all treatment groups (Table 12). The mean gains in VA increased rapidly after the first injection in all treatment groups and then steadily increased and was maintained throughout the 1-year follow-up. The integrated mean gain in BCVA letters at 12-month follow-up in the following groups was 9.3 letters (2.0 mg of aflibercept monthly), 8.7 letters (0.5 mg ranibizumab monthly), 8.4 letters (2.0 mg of aflibercept bimonthly), and 8.3 letters (0.5 mg aflibercept monthly). The bimonthly aflibercept dosing strategy resulted in a mean VA gain within 0.3 letters (with a confidence interval of < 2 letters) of the monthly doses of ranibizumab.

Central retinal thickness as assessed by OCT decreased rapidly even by the first month, in all groups. A post hoc analysis evaluated differences in percentage of fluid-free or dry retina (OCT-defined absence of both cystic and intraretinal edema and SRF) at follow-up with the various drugs and dosing. All aflibercept groups were similar to the monthly doses of the ranibizumab group with numerically better control (fluid-free) in the aflibercept higher dose at monthly and bimonthly dosing (Table 12). The integrated analysis showed percentages of fluid-free retina ranging from 60.3% (aflibercept 2.0 mg monthly), 62.0% (ranibizumab 0.5 mg monthly), 67.7% (aflibercept 2.0 mg bimonthly), and 72.4% (aflibercept 0.5 mg monthly).

In the second year the dosing intervals for all treatment groups were changed to a common protocol (maintaining the original drug and dose assignment) that included a capped monthly PRN re-treatment with a minimum 3-month re-treatment frequency interval. (69) Re-treatment was based on the occurrence of any 5 criteria: loss of ≥ 5 ETDRS letters and OCT-based recurrent fluid; OCT new or persistent fluid; new-onset classic neovascularization; FA new or persistent leak; or new macular hemorrhage. During the 2-year follow-up, there were 16.0, 16.2, and 16.5 injections in the monthly 0.5 mg of aflibercept, 2.0 mg of aflibercept, and 0.5 mg of ranibizumab dosing groups, respectively, compared with the 11.2 injections in the 2.0-mg bimonthly aflibercept injection group. In the second year of follow-up under the PRN re-treatment protocol, there were 4.2 injections for the aflibercept group and 4.7 for the ranibizumab group. This was achieved with similar stabilization in VA gains from 91% to 92% across the groups. The improvements in retinal thickness were also largely maintained over the 2 years in all treatment groups (data not shown).

Table 12: Effect of Re-treatment Strategies on Outcomes in Aflibercept Versus Ranibizumab RCTs for n-AMD

Outcomes	VIEW 1			VIEW 2				
	Ranibi-zumab 0.5 mg Monthly	Aflibercept 2 mg Monthly	Aflibercept 0.5 mg Monthly	Aflibercept 2 mg Monthly	Ranibizumab 0.5 mg Monthly	Aflibercept 2 mg Monthly	Aflibercept 0.5 mg Monthly	Aflibercept 2 mg Bimonthly
Number in PP (ITT)	269 (304)	285 (304)	270 (301)	265 (301)	269 (291)	274 (309)	268 (296)	270 (306)
Proportion (%) maintaining vision in PP analysis (losing < 15 ETRDS letters)	94.4	95.1	95.9	95.1	94.4	95.6	96.3	95.6
Proportion (%) maintaining vision in ITT analysis (losing < 15 ETDRS letters)	93.8	95.1	95.0	94.4	94.8	94.5	95.3	95.4
Δ ETDRS BCVA letters, mean ± SD	8.1 ± 15.3	10.9 ± 13.8	6.9 ± 13.4	7.9 ± 15.0	9.4 ± 13.5	7.6 ± 12.6	9.7 ± 14.1	8.9 ± 14.4
Proportion (%) gaining (≥ 15 letters) vision (ITT analysis)	30.9	37.5	24.9	30.6	34.0	29.4	34.8	31.4
Δ CNV area, mm mean ± SD	−4.2 ± 5.6	−4.6 ± 5.5	−3.5 ± 5.3	−3.4 ± 6.0	−4.2 ± 5.9	−6.0 ± 6.1	−4.2 ± 6.1	−5.2 ± 5.9
Δ CRT, µm mean ± SD	−116.8 ± 109.0	−116.5 ± 98.4	−115.6 ± 104.1	−128.5 ± 108.5	−138.5 ± 122.2	−156.8 ± 122.8	−129.8 ± 114.8	−149.2 ± 119.7
Proportion (%) dry retina (absence of cystic intraretinal edema and SRF on OCT)	63.6	64.8	56.7	63.4	60.4	80.3	63.9	71.9

Abbreviations: BCVA, best corrected visual acuity; CNV, choroidal neovascularization; CRT, central retinal thickness; ITT, intention to treat; OCT, optical coherence tomography; PP, per protocol; SD, standard deviation; SRF, subretinal fluid.

Section C. PRN Re-treatment Strategies for n-AMD in Single-Arm A-VEGF Trials

The efficacy of various as-needed or PRN ranibizumab dosing schedules for n-AMD was evaluated in several prospective single-arm studies in clinical practices in various countries (Table 13). The studies examined variable dosing strategies for the loading dose phase, employing 1-month (70;71) or 3-month (47;72-74) monthly loading dose injections followed by various monitoring and as-needed re-treatment strategies in the subsequent maintenance phase. In most trials, monthly visits with various combinations of VA testing, medical exams, ophthalmologic exams, fundus photography, and OCT were performed. Fluorescein angiography (FA) was generally performed more selectively, at baseline and when clinical or other imaging findings were uncertain. The actual number of visits or imaging exams performed was generally not reported.

Re-treatment criteria varied across the studies, but changes in quantitative OCT measures of retinal anatomy, usually an increase in CRT, or decreases in VA were common re-treatment criteria. Qualitative measures, such as leakage, hemorrhage, or criteria suggestive of macular fluid (retinal cysts, SRF, or PED enlargement), were often cited as additional considerations for re-treatment.

Table 13: Study Characteristics of Single-Arm A-VEGF Treatment Trials for n-AMD

Study, Author, Year, Country	Study Design and Follow-Up	Sites, Patients, Trial Arms	Maintenance and Follow-Up	Re-treatment Criteria
Kang , 2009, (70) Korea	Prospective cohort study 1 year	1 site, 60 P 0.5-mg 1MoLD of ranibizumab and PRN re-treatment	Monthly visits with fundus examination, BCVA, IOP. OCT, and FA performed every 2–3 months	1) Decreased VA associated with increased CNV leakage assessed by FA or by OCT, 2) increased CRT, 3) appearance of new macular hemorrhage and SRF
Gerding et al, 2011, (72) Switzerland	Retrospective cohort study 1 year	1 site, 104 P 0.5-mg 3MoLD of ranibizumab and PRN re-treatment	Monthly visits with BCVA, anterior and posterior segment biomicroscopy, IOP, and OCT. FA at baseline, 3 months after first injection, and at examiners' discretion	1) Decreased VA ≥ 1 line associated with any OCT or FA signs of exudative AMD, 2) persistent or newly developed SRF, IRF-filled spaces, 3) increase CRT < 100 µm, 4) new SRF hemorrhage, 5) signs of active neovascular disease on FA
Heimes et al, 2011, (73) Germany	Retrospective cohort study 75 weeks	1 site, 145 P 3MoLD of ranibizumab and PRN with 3 re-treatments	Follow-up at weeks 12, 24, 48, and 60 with BCVA and OCT	1)Decreased VA 2) increased CRT (> 100 µm) on OCT 3) new leakage on FA 4) new retinal hemorrhage
PrONTO, Fung et al, 2007, (46) Lalwani et al, 2009 (47) United States	Prospective cohort study 2 years	1 site, 40 P 0.5-mg 3MoLD of ranibizumab and PRN re-treatment	VA testing and ophthalmoscopic exams (baseline, days 14, 30, 45, 60, and monthly afterward); fundus photography and OCT imaging (baseline, days 1, 2, 4, 7, 14, and 30 after first 2 monthly injections and then monthly) and FA (baseline, months 1, 2, 3, and every 3 months afterward)	Any 1 of the following 5 occurrences between intervals: 1) BCVA loss of ≥ 5 letters with OCT-detected macular fluid, 2) increased CRT (distance between inner and outer boundaries) ≥ 100 µm; 3) new-onset hemorrhage, 4) new classic CNV; 5) persistent fluid following last injection. In year 2 amendments to re-treatment criteria included any qualitative change (retinal cysts, SRF, or PED enlargement) on OCT suggestive of recurring macular fluid
Rothenbuehler et al, 2009, (71) Switzerland	Prospective cohort study 2 years	1 site, 138 P 0.5-mg 1MoLD of ranibizumab and PRN re-treatment	Monthly visits including full medical and ocular history, BCVA, binocular ophthalmoscopy, colour fundus photography, and OCT. FA at baseline and at 3-month intervals	1) Presence of SRF, intraretinal edema, or sub-RPE on OCT; 2) CRT increased by more than 10% of preceding value; 3) signs of active leaking CNV on FA (increased leakage of lesion, new hemorrhage); 4) ETDRS BCVA decreased > 5 letters and increased metamorphosia; 5) new SRF or IRF hemorrhage
SUSTAIN, Holz et al, 2011, (74) European countries and Australia	Phase III open-label multicentre prospective study 1 year	10 sites, 513 P 0.5-mg 3MoLD of ranibizumab and PRN re-treatment	Assessments included vital signs assessment, standard ophthalmic examinations, and tonometry at screening, baseline, day 8, and months 1, 2, 3, and 12 and (optionally) from months 4–11. Colour fundus photography and FA were done at screening, baseline, and months 3 and 12 and were optional at months 6 and 9. IOP, indirect ophthalmoscopy, and slit-lamp examination before each study treatment	1) VA decreased > 5 letters 2) CRT increased > 100 µm

Abbreviations: AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CNV, choroidal neovascularization; CRT, central retinal thickness; FA, fluorescein angiography; IOP, intraocular pressure; IRF, intraretinal fluid; 1MoLD, 1-month loading dose; 3MoLD, 3-month loading dose; OCT, optical coherence therapy; P, patient; PED, pigment epithelium detachment; PRN, pro re nata (as needed); RPE retinal pigment epithelium; SRF, subretinal fluid; VA, visual acuity.

Generally the trials all reported a reduction (compared with monthly regimens) in the mean number of ranibizumab reinjections performed in the maintenance phase of the first year of follow-up with their various PRN re-treatment strategies (Table 14). The ranges reported for the reinjections, however, varied from requiring only the loading dose injections to requiring monthly injections. The 2 studies with 2-year follow-up (47;71) both reported fewer reinjections on average in the second year than the first year. All of the studies reported parallel improvements in retinal thickness; CRT values generally decreased > 100 µm.

The SUSTAIN trial with more than 500 n-AMD patients was the largest trial evaluating a PRN re-treatment strategy. Re-treatment in this study was based mainly on VA declines or OCT quantitative increases in retinal thickness. Although this strategy resulted in a halving of the monthly reinjections, it was associated with a range of reinjections and much lower visual gains (3.6 BCVA letters) at follow-up than those reported with ranibizumab monthly doses in MARINA (7.2 letters) and ANCHOR (11.3 letters). The OCT/VA–guided re-treatment criteria in the trial could also have been limited by relying solely on defined quantitative measures of retinal thickness and VA change. In the PrONTO trial, investigators noted the same limitation with quantitative re-treatment criteria and in the second year of the trial amended re-treatment criteria to include any qualitative signs of recurrent macular fluid resulting in an even greater VA improvement over baseline: 11.1 BCVA letters at 2-year follow-up compared with 9.3 BCVA letters at 1-year follow-up. (47)

Table 14: PRN A-VEGF Re-treatment Strategies for n-AMD in Single-Arm Trials

Study, Author, Year	Δ ETDRS BCVA Letters Mean ± SD	Proportion (%) Gaining ≥ 15 BCVA Letters	Proportion (%) Losing ≥15 BCVA Letters	Δ CRT (µm) Mean (range)	Visits and OCT Exams	Injections Mean ± SD Median (Range)
Kang et al , 2009 (70)	0.158 logMAR Snellen chart	NR	14	−107.7	Fixed monthly visits, OCT exams every 2–3 months	4.2 (R, 1–6)
Gerding et al, 2011 (72)	5.0	47	22	−93.0	Fixed monthly visits and OCT exams	5.8 ± 2.3 (R, 3–11)
Heimes et al, 2011 (73)	0.61 ± 0.36 logMAR	NR	NR	−90 over 12 weeks	NR	5.0 ± 1.97 (R, 3–10)
PrONTO, Fung et al, 2007 (46) Year-1	9.3 11 median	35	3	−178	Fixed monthly visits and OCT exams	5.6 ± 2.3 5.0 (R, 3–13)
PrONTO, Lalwani et al, 2009 (47) Year-2	11.1 ± 12.2 14 median	45	0	−212 Median −209	Fixed monthly visits and OCT exams	9.9 ± 5.3 9.0 (R, 3 − 25)
Rothenbuehler et al, 2009 (71)						
Year 1	7.3 ± 14.5	31	8	−151 (R,−95 to −237)	Fixed monthly visits and OCT exams	5.6 ± 2.9 (R, 3–11)
Year 2	6.3 ± 14.5	30	15	−212 (R, −103 to −45)	Fixed monthly visits and OCT exams	4.3 ± 3.8 (R, 1–8)
SUSTAIN, Holz et al, 2011 (74)	3.6 ± 13.9	19	4	−91.5	Fixed monthly visits and OCT exams	5.6 ± 2.37 (R, 1–12)

Abbreviations: BCVA, best corrected visual acuity; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; logMAR, logarithm of the minimum angle of resolution; NR, not reported; OCT, optical coherence tomography; R, range; SD, standard deviation.

Treat-and-Extend PRN Re-treatment Strategy

A treat-and-extend strategy, a special form of a PRN re-treatment schedule for A-VEGF treatment for n-AMD, was first proposed by Richard Spaide. (75) The proposal was aimed at reducing re-injections and visits and involved a strategy of gradually extending the duration of the subsequent follow-up visit if there were no signs of active disease (such as new hemorrhage) or signs of exudation (such as edema or SRF). Reinjection was to be performed in the signs of active disease and the follow-up visit interval shortened. This approach was evaluated by 3 investigators using different re-treatment protocols in small single-site studies (Table 15). (76-78)

Table 15: Study Characteristics of Treat-and-Extend PRN Re-treatment Protocols for n-AMD in A-VEGF Trials

Study, Author, Year, Country	Study Design and Follow-Up	Sites, Patients, Trial Arms	Maintenance and Follow-Up	Re-treatment Criteria
Ernst et al, 2010 (76) United States	Single-arm prospective study 1 year	1 site, 22 Ps 0.5 mg of ranibizumab monthly until OCT-based CRT failed to decrease followed by treat-and-extend PRN	Maximum 3-month visit interval with OCT and Snellen VA testing	Any recurrence of fluid on OCT, such as retinal cysts, SRF, or increase in CRT > 100 µm
LAST, Fung et al, 2012 (77) United States	Single-masked prospective RCT 6 months	1 site, 9 Ps Low- (0.5-mg) vs. high- (2.0-mg) dose 3MoLD of ranibizumab followed by treat-and-extend PRN	Maximum 2-month visit interval with SD-OCT and ETDRS BCVA testing	After a 4-week post–loading dose phase, patients were reinjected if SRF or IRF were present on SD-OCT and then reviewed again in 4 weeks. If no SRF or IRF was present, patients were re-evaluated at 2-week intervals or if SRF or IRF was present patients received treatment at 6 weeks or at 8 weeks regardless of fluid present. Any recurrence of fluid required a review shortened to 4 weeks following an injection. Recurrence or increase in vascularized PED was also re-treatment indication
Oubraham et al, 2011 (78) France	2 parallel cohorts 1 year	1 site, 90 Ps Group 1: 3MoLD of ranibizumab followed by PRN re-treatment Group 2: 3MoLD of ranibizumab followed by treat-and-extend PRN	Maximum 3-month visit interval with SD-OCT, fundus photography, and EDTRS BCVA	In the PRN treatment group, subsequent injections were given with VA decreased > 5 letters, persistent subfoveal or perifoveal fluid, macular IRF on OCT, or new hemorrhage In the treat-and-extend group, patients were examined at 6 weeks post–loading dose and treated regardless of OCT. The next visit was scheduled 8 weeks later if OCT and fundus photography did not show exudative manifestations (subfoveal or perifoveal fluid or macular edema) or new macular hemorrhage—or at 4 weeks if they did. Those with no signs of active disease at week 8 were examined and re-treated 10 weeks later and, in absence of active CNV, at week 10. Follow-up for any interval was not extended beyond 12 weeks

Abbreviations: BCVA, best corrected visual acuity; CNV, choroidal neovascularization; CRT, central retinal thickness; IRF, intraretinal fluid; 3MoLD, 3-month loading dose; OCT; optical coherence tomography; P, patient; PED, pigment epithelium detachment; PRN, pro re nata (as needed); RCT, randomized controlled trial; SD-OCT, spectral domain optical coherence tomography; SRF, subretinal fluid; VA visual acuity.

The mean number of ranibizumab reinjections with the treat-and-extend re-treatment protocol was reduced over the monthly injections but was similar to mean numbers reported for regular PRN monitoring protocols (Table 16). The treat-and-extend protocol was also associated with variability in reinjections similar to variability in the usual PRN protocol ranging from loading dose only to monthly reinjections. The improvements in the CRT with treat-and-extend strategies, when reported, were much lower than improvements associated with regular PRN monitoring, which were usually 100 µm or more at follow-up. The Oubraham et al study (78) was the only one to have a comparative group of the PRN strategies, which in this study included regular monthly follow-up and PRN testing. In this cohort study patients with n-AMD were recruited to a treat-and-extend ranibizumab protocol and compared with a group of patients previously treated with the regular PRN re-treatment protocol. The mean number of 8.8 visits in their PRN group was also associated with a much lower mean VA gain than the treat-and-extend group: 2.3 letters versus 10.8 letters.

Table 16: Treat-and-Extend PRN Re-treatment Protocols for n-AMD on Outcomes in A-VEGF Trials

Study, Author, Year	Δ BCVA Letters Mean ± SD	Proportion (%) Gaining ≥ 15 BCVA Letters	Proportion (%) Losing ≥ 15 BCVA Letters	Δ CRT (µm) Mean ± SD	# Visits Mean ± SD (Range) 12 Months	# Injections Mean ± SD (Range) 12 Months
Ernst et al, 2010 (76)	1.6 ± 2.9 (Snellen) 8 letters	36	12	−43	NR	6.0 ± 2.7 (3–12) Over 16 months
LAST, Fung et al, 2012 (77)						
High- vs. low-dose ranibizumab	4.1 ± 4.5 vs. 3.0	NR	NR	−28 ± 46 vs. −73	NR	6.0 vs. 5.0
Oubraham et al, 2011 (78)						
PRN group	2.3 ± 17.4	NR	NR	NR	8.8 ± 1.5 (6–13)	5.2 ± 1.9 (3–10)
Treat-and-extend group	10.8 ± 8.8	NR	NR	NR	8.5 ± 1.1 (7–12)	7.8 ± 1.3 (6–11)

Abbreviations: BCVA, best corrected visual acuity; CRT, central retinal thickness; NR, not reported; PRN, pro re nata (as needed); SD, standard deviation.

Section D. Long-Term Outcomes of PRN Re-treatment Strategies for n-AMD in A-VEGF Trials

The longer-term (> 2 years) maintenance of VA gains in ranibizumab-treated n-AMD patients was evaluated in 4 trials (Table 17). (79-82) Two of the trials, the SECURE by Silva et al (81) and the HORIZON by Singer et al (82), known as extension trials, included subjects who completed previously conducted RCTs. The SECURE trial was an integrated 2-year follow-up study of patients who completed 1 year of the EXCITE (43) and the SUSTAIN (74) studies providing 3-year follow-up. The HORIZON study was an integrated 1-year follow-up study of patients who completed 2 years of 3 prospective 2-year RCT studies: the MARINA, (19) ANCHOR, (20;21) and FOCUS (83;84) studies. Two other studies (79;80) examined longer-term VA maintenance in single-site institutional reviews providing 3-year (80) and 4-year (79) PRN A-VEGF follow-up after VEGF treatment for n-AMD.

Table 17: Study Characteristics of PRN A-VEGF Re-treatment Strategies for n-AMD in Long-Term Extension Trials

Study, Author, Year, Country	Study Design and Follow-Up	Sites, Patients, Trial Arms	Follow-Up Protocols	Re-treatment Protocol
SECURE, Silva et al, 2013 (81) Europe and Australia	Integrated follow-up of completers of 2 prior RCTs 3 years	SECURE: 41 sites, 10 countries, 234 Ps 0.5 mg of ranibizumab PRN, no more frequently than monthly (100/531 Ps from SUSTAIN RCT, 134/353 from EXCITE RCT) Followed by VA-guided PRN retreatment strategy	Monthly monitoring included ETDRS BCVA. OCT was not mandated by protocol and was performed at investigators' discretion. Standard ophthalmic examinations were performed every 6 months including tonometry, indirect stereo ophthalmoscopy, and slit-lamp stereoscopic fundus biomicroscopy. Vital signs (systolic and diastolic blood pressure) and IOP was measured at 6-month visits and before any ranibizumab injections	Loss of > 5 ETDRS BCVA letters
HORIZON, Singer et al, 2012 (82) United States	Integrated follow-up of completers of 3 prior RCTs 4 years	HORIZON (853/1,301 Ps) (MARINA n = 716, ANCHOR n = 423, FOCUS n = 162)	Quarterly mandated visits (with discretional interval visits allowed) included physical examinations, eye exams, ETDRS BCVA, vital signs, and incidence of serum antibodies to ranibizumab. IOP was measured before injections	Re-treatment was at investigators' discretion. There were no prescribed re-treatment criteria based on VA, OCT, FA, or other objective measure
Kruger et al, 2013 (79) Denmark	Retrospective single-centre study 4 years	1 site, 855 Ps 0.5-mg 3MoLD of ranibizumab and PRN re-treatment strategy	Follow-up visits conducted approximately monthly included ETDRS BCVA, funduscopy, and OCT. FA was reserved for unusual cases or treatment responses	Re-treatment followed national guidelines from Danish Ophthalmological Society. Treatment was terminated if no signs of disease activity 6 months after last injection or if BCVA had deteriorated after 3–6 injections
Muniraju et al, 2013 (80) United Kingdom	Retrospective single-centre study 3 years	1 site, 156 Ps 0.5-mg 3MoLD of ranibizumab and PRN re-treatment strategy	Follow-up schedule unreported, but visits included VA and OCT testing	Re-treatment based mainly on OCT-defined persistence, increased or new SRF and intraretinal edema, subretinal or intraretinal hemorrhage

Abbreviations: BCVA, best corrected visual acuity; FA, fluorescein angiography; IOP, intraocular pressure; 3MoLd, 3-month loading dose; OCT, optical coherence tomography; P, patient; PRN, pro re nata (as needed); RCT, randomized controlled trial; SRF, subretinal fluid; VA, visual acuity.

The long-term outcomes of the trials are summarized in Table 18. Re-treatment criteria in the trials varied with only the Muniraju et al (80) study defining OCT as the main re-treatment criteria. Neither of the extension trials was based on OCT-guided re-treatment. All of the studies reported on vision outcomes with long-term PRN-guided A-VEGF treatment—none reported on retinal anatomic outcomes such as CRT.

SECURE Extension Trial

The SECURE (81) study was primarily designed to assess long-term safety and efficacy of A-VEGF (0.5 mg of ranibizumab) for n-AMD patients. The patients recruited in this study had been treated differently

in the previous RCTs. In the EXCITE trial, patients were randomized to 3 groups after 3 months' administration of monthly loading doses of 0.3 mg or 0.5 mg of ranibizumab to fixed quarterly or monthly treatments in the following 9-month maintenance period. All patients in the SUSTAIN trial, however, had been treated with a VA and OCT-guided PRN re-treatment strategy in the maintenance period after the 3-month loading dose of 0.3 mg of ranibizumab.

Going forward in the 2-year SECURE extension trial, patients with n-AMD were an average of 75 years old and were to be followed and treated on a VA-guided PRN basis. Ten percent of the study participants did not complete the study follow-up. The initial improvements seen in all treatment groups in the previous trials declined over time in the 2-year follow-up of the SECURE trial. Overall there was a mean ETDRS BCVA decline of −4.3 ± 13.04 (95% CI, −6.0 to −2.6) letters at 2-year follow-up over the SECURE baseline. The decline in the BCVA occurred in all trial subgroups. In the previous EXCITE trial study arms of fixed quarterly doses of 0.3 mg and 0.5 mg of ranibizumab and monthly 0.3 mg of ranibizumab, mean VA losses at 2-year follow-up were −3.6 ± 11.89 letters, −5.5 ± 11.94 letters, and −5.9 ± 15.61 letters, respectively.

In the SUSTAIN trial with OCT- or VA-guided PRN re-treatment protocol, the mean VA loss was −3.6 ± 12.94 letters. Overall in the SECURE trial, a mean number of 6.1 ± 5.67 (3.4 in year 2 and 2.8 in year 3) and median number of 4 (R, 0–24) reinjections were administered in the 2-year follow-up. It was also noted that 42% of the patients had 7 or more visits at which injections were not performed when VA loss of > 5 lines occurred (over highest value ever achieved in previous study) suggesting either under-treatment or other factors influencing re-treatment. Decreased visits, imprecise re-treatment criteria or their application, and gradual macular atrophy could all have also contributed to declining VA over the study duration.

HORIZON Extension Trial

The HORIZON (82) study was also designed to evaluate the long-term efficacy and safety of ranibizumab intravitreal injections of patients with n-AMD. Participants in the 3 prior RCT studies receiving different intervention protocols, but all involving monthly injections, yielded 3 different patient streams for the HORIZON study—those initially treated with ranibizumab (n = 600), those previously in the control group who crossed over to receive ranibizumab (n = 190), or those untreated with ranibizumab (n = 63). Although quarterly follow-up visits were initially mandated, protocols were changed to quarterly visits (most participants were seen every 2 months), and re-treatment over the study follow-up was not by protocol but left to the discretion of the investigator. Thirty-two percent of participants did not complete the study's 2-year follow-up.

The mean BCVA of the previously treated ranibizumab patients slowly declined over study follow-up, from 9.0 letters at HORIZON baseline to 4.0 letters at 3 years, 2.0 letters at 4 years, and −0.1 letters at 5 years. The group not treated with ranibizumab in the original studies, who had lost VA (−9.6 letters) over their baseline at the end of the prior trial and at entry to the HORIZON trial, continued to lose BCVA throughout the study. Visual loss in this group declined over their HORIZON baseline at follow-up to −11.8 letters (2.2-letter loss) at 3 years, −11.8 letters (stable) at 4 years, and −16.1 letters (−6.5 letters) at 5 years.

Patients initially treated with ranibizumab received a mean number of 27.5 ± 5.5 injections over the 5-year follow-up (2 years in the initial trial and 3 years in the HORIZON study). During the HORIZON follow-up, a mean number of 4.4 ± 5.3 reinjections were performed, cumulatively 2.2 (year 1), 4.2 (by year 2) and 4.3 (by year 3). Cumulative visits and reinjections in the HORIZON 3-year follow-up were compared for patients gaining ≥ 15 BCVA letters—(mean 12.5 visits R, 7.0–23.0) and (mean 4.1 re-injections R, 0–21—and for patients losing ≥ 15 BCVA letters—(mean 11.8 visits R, 7.0–18.0) and (mean 4.1 re-injections R, 0–13).

Table 18: Outcomes of A-VEGF Re-treatment Strategies for n-AMD in Long-Term Extension Trials

Study Assessment Period	Δ ETDRS BCVA Letters Mean ± SD	Proportion (%) Gaining ≥ 15 BCVA Letters	Proportion (%) Losing ≥ 15 BCVA Letters	# Visits Mean	# Injections Mean ± SD
SECURE (81)					
Year 2 (over SUSTAIN base)	−2.0 ± 10.44	26.2	13.3	NR	3.4
Year 3 (over SUSTAIN base)	−4.3 ± 13.04	23.6	18.9	NR	2.8
HORIZON (82)					
Year 3 (over HORIZON base)	−2.2	NR	NR	NR	2.2
Year 4 (over HORIZON base)	−2.2	3.1	24.7	NR	4.2
Year 5 (over HORIZON base)	−6.5	NR	NR	NR	4.3

Abbreviations: BCVA, best corrected visual acuity; NR, not reported; SD, standard deviation.

Single-Site Prospective Long-Term Follow-up Cohort Studies

Kruger et al (79) prospectively surveyed n-AMD patients treated with ranibizumab at a single centre in Denmark using a PRN re-treatment scheme based on national guidelines. The study evaluating visual outcomes and quit rates included 855 patients whose mean age was 76 years (range, 55–98 years) receiving ranibizumab over a 4-year period during which 399 (47%) discontinued treatment. Discontinuation occurred throughout the study follow-up with most patients dropping out within the first 2 years—157 (18%) in the first year, 174 (20%) in the second year, 55 (6%) in the third year, and 13 (2%) in the fourth year. The reasons for discontinuing treatment included no signs of disease activity (45%, 181/399); judged non-treatable by the physician (28%, 113/399); could not complete follow-up (17%, 69/399); patients no longer wanted treatment (9%, 36/399).

The overall treatment effect was a mean loss of 2.7 BCVA letters at last follow-up with a mean number of 8.7 injections (range, 1–35) during a mean 23.3-month follow-up (Table 19). Those gaining (17%, 142/855) or losing (23%, 198/855) ≥ 15 BCVA letters received a similar mean number of injections: 8.2 and 8.1, respectively. Patients who discontinued treatment were much more likely to have lost (33%, n = 132) rather than gained (15%, n = 61) ≥ 15 BCVA letters. Patients judged to be non-treatable had a worse BCVA at baseline than others; at baseline 10% of these patients recognized fewer than 20 letters, and after treatment, 48% recognized fewer than 20 letters. Overall, 21% (181/855) were reported to have discontinued treatment because of complete inactivation of their CNV, and 15% (131/855) did not respond to treatment, leaving most (64%) in need of continuous treatment.

The second single-centre study, a study in the United Kingdom by Muniraju et al (80), followed 156 n-AMD patients (mean age 82 years; range, 55–97) treated with ranibizumab for 3 years with a PRN re-treatment strategy based on OCT findings. The overall mean BCVA change over baseline slowly declined over the 3-year follow-up from 3.0 letters at 1 year to 0.9 letters at 3 years and was associated with decreasing annual mean injection numbers: 4.8 in the first year, 2.9 in the second year, and 2.4 in the third year.

Improvements in VA over time when stratified by baseline VA (≤ 35 letters, 36–54 letters, and ≥ 55 letters) showed 3 response patterns—gains (23%), partial gains (35.1%), and no gains (41.9%). Those with the poorest VA at baseline (≤ 35 letters) showed the most VA improvement at 1 year (9.2 ± 19.2 letters) that remained high at 2-year (6.6 ± 21.1 letters) and 3-year (6.5 ± 20.3 letters) follow-up. Those with baseline VA between 36 and 54 letters initially gained VA at 1 year (4.5 ± 15.1 letters) that slowly declined over the 2-year (2.6 ± 19 letters) and 3-year (1 ± 20.1 letters) follow-up. The third group with the

best VA at baseline (≥ 55 letters) was stable with no VA gains at 1-year (−0.5 ± 11 letters) and at 2-year (−0.5 ± 11.9 letters) follow-up and gradually declined (−2.4 ± 14.9 letters) in the third year.

Table 19: Long-Term Outcomes of PRN A-VEGF Re-treatment Strategies for n-AMD in Cohort Studies

Follow-Up Period	Δ ETDRS BCVA Letters Mean ± SD	Proportion (%) Gaining ≥ 15 BCVA Letters	Proportion (%) Losing ≥ 15 BCVA Letters	# Visits	# Injections Mean ± SD
Kruger et al (79)					
4-year last observation	−2.7	17.0	23.0	NR	8.7 (R, 1–35)
Muniraju et al (80)					
Year 0–1	3.0	20.1	9.8	NR	4.8 ± 2.2
Year 0–2	2.2	20.7	14.4	NR	7.8 ± 4.2
Year 0–3	0.9	19.0	19.0	NR	10.6 ± 6.2

Abbreviations: BCVA, best corrected visual acuity; NR, not reported; PRN, pro re nata (as needed); R, range; SD, standard deviation.

Section E. Monitoring Effectiveness in Real-World Clinical Management

The effectiveness of A-VEGF PRN re-treatment strategies for n-AMD patients in real-world clinical practice settings was evaluated in several studies conducted in various countries. (85-92) These studies, usually involving the practices of retinal specialists affiliated with academic hospital centres, are summarized in Table 20. Studies of usual or routine clinical care differ from clinical trials in several ways. In general, physicians providing routine care tend to have fewer restrictions and studies of their practices include patients with a wider range of VA, having more difficult-to-treat retinal conditions, such as retinal angiomatous proliferation, and having more ocular comorbidity.

The as-needed or PRN approach to re-treatment employed in all of these studies was expected not only to reduce treatment burden but also to avoid over-treatment and its cumulative risks by individualizing patient treatment on the basis of clinical characteristics rather than on fixed protocol approach of trials. The follow-up schedules and PRN treatment strategies (Table 20) followed by the treating physicians were variable and loosely defined by a range of qualitative and quantitative clinical and retinal anatomic re-treatment criteria.

Table 20: Real-World Clinical Management Studies of A-VEGF Treatment of n-AMD

Author, Year, Country	Study Design and Follow-Up	Sites, Patients, Trial Arm	Follow-Up	Re-treatment Criteria
Bandukwala et al, 2010 (85) Ontario, Canada	Nonrandomized consecutive retrospective chart review 1 year	1 academic site, 3 RPs; 94 Ps 3MoLD 0.5 mg ranibizumab and PRN re-treatment	Every 4–6 weeks or longer depending on physicians' discretion and patient availability	1)Persistent SRF 2) new macular hemorrhage 3) macular intraretinal edema or 4) worsening VA
Carneiro et al, 2012 (86) Portugal	Retrospective consecutively treated cohorts 1 year	1 academic site, 186 Ps 1.25-mg 1MoLD of bevacizumab and PRN re-treatment (all treated before 2008) vs. 0.5-mg 3MoLD of ranibizumab and PRN re-treatment (all treated after 2008)	Follow-up at months 1, 2, 3, 4, 5, 6, 9, and 12 included ETDRS BCVA, funduscopic examination, and OCT	1) Macular hemorrhage 2) presence of SRF or IRF on OCT or 3) leakage on FA. Reinjections were performed 5–7 days after medical visit
Cohen et al, 2009, (87) 2012 (93) France	Retrospective multicentre chart review 1 year	3 academic sites, 6 RPs at Site 1, 1 RP at Sites 2 and 3; 290 Ps Site 1: 1MoLD (4 RPs) or 3MoLD (2 RPs) of ranibizumab and treat-and-extend maintenance Sites 2 and 3: 1MoLD of ranibizumab and PRN re-treatment	Site 1 (treat and extend), Sites 2 and 3 (PRN); visits included ETDRS BCVA, fundus ophthalmoscopy and photography, and OCT	Re-treatment protocol same across sites:1) persistent subfoveal or perifoveal fluid 2) macular intraretinal edema 3) BCVA > 5 letters or 4) occurrence of new hemorrhage. In the absence of re-treatment criteria, exams were rescheduled 5–6 weeks later and then gradually spaced out
Dadgostar et al, 2009 (88) United States	Retrospective interventional case series 1 year	1 private site, 124 Ps 0.5-mg 1MoLD of ranibizumab and PRN re-treatment	Serial clinical exams (interval not specified), Snellen BCVA, and OCT	1)Increased retinal thickening 2) IRF, SRF, intraretinal cysts, or 3) increasing PED
Katz et al, 2012 (89) Ontario, Canada	Retrospective cohort study 1 year	1 academic site, 2 RPs, 56 Ps RP 1: 0.5-mg 1MoLD of ranibizumab and monthly re-treatment RP 2: 0.5-mg 3MoLD of ranibizumab and treat-and-extend PRN re-treatment	Visits in treat-and-extend group were increased to a maximum of 2 months. Serial clinical exams included Snellen BCVA and every 4 months dilated funduscopy, repeat OCT, and FA	1)Any SRF or IRF on OCT or 2) any subretinal hemorrhage on dilated funduscopy
Kumar et al, 2011 (90) United Kingdom	Prospective cohort study 1 year	1 academic site, 81 Ps 0.5-mg 3MoLD of ranibizumab and PRN re-treatment	Serial clinical exams (interval not specified) included ETDRS BCVA, OCT	Deterioration in signs or symptoms included 1) decreased BCVA (5–19 letters) 2) worsening IRF or SRF or 3) fresh hemorrhage or extension of lesion on FA. Criteria were also included for cessation of treatment: 1)symptoms no better or worse 2) loss ≥ 30 letters over baseline 3), SRF absent or persistent but unresponsive to prior treatments 4), structural damage on OCT 5) fibrosis > 75% of the lesion involving the fovea or 6) serious adverse event
Michalova et al, 2009 (91) Australia	Retrospective chart review 1 year	1 academic site, 4 RPs, 158 Ps 0.3 mg of ranibizumab (after April 2007 0.5 mg) and PRN re-treatment	No general protocol stated, serial clinical exams (interval not specified) included Snellen BCVA and OCT	Individual clinician judgment, re-treatment criteria not stated
Muether et al, 2013 (92) Germany	Prospective interventional case series 1 year	1 academic site, 89 Ps 3MoLD of ranibizumab and PRN re-treatment 3 times with recurrent disease activity	Monthly visits included ETDRS BCVA, SD-OCT. FA performed only when CNV activity was questionable on SD-OCT images	PrONTO criteria; 1) recurrence of any SRF or cystic maculopathy on OCT in previously dry macula 2) CRT increased > 100 µm, 3) new area of classic CNV 4) new hemorrhage or 5) BCVA decreased 5 letters (from highest BCVA) and associated with leakage on FA or fluid on OCT

Abbreviations: BCVA; best corrected visual acuity; CNV, choroidal neovascularization; CRT, central retinal thickness; FA, fluorescein angiography; IRF, intraretinal fluid; 1MoLD, 1-month loading dose; 3MoLD, 3-month loading dose; OCT, optical coherence tomography; P, patient; PED, pigment epithelium detachment; PRN, pro re nata (as needed); RP, retinal practices; SD-OCT; standard fluence optical coherence tomography; SRF, subretinal fluid; VA, visual acuity.

The results of these observational studies are outlined in Table 21. Two of the studies (85;89) were conducted in Canada and involved group practices of retinal specialists. In the Bandulkwala et al study, (85) all specialists at one centre employed similar PRN re-treatment strategies. In the Katz et al study, (89) specialists performed monthly or PRN re-treatment strategies. The variation in the mean VA gains with 1-year follow-up across retinal practices (85) where specialists used similar re-treatment protocols was noteworthy, ranging from a loss of 2.9 letters (with 3.3 reinjections) to a gain of 10.7 letters (with 5.2 reinjections). In the Katz et al study, (89) in which VA gains were compared between PRN-guided and monthly treatment protocols, lower mean VA gains were reported in patients receiving PRN than those receiving monthly injections at their site. The French study by Cohen et al (87) also reported great variability in mean VA gains across multiple retinal practices at 3 sites.

Table 21: Outcomes in Real-World Clinical Management Studies of A-VEGF Treatment of n-AMD

Author, Year, Study Group	Δ ETDRS BCVA Letters Mean ± SD	Proportion (%) Gaining ≥ 15 BCVA Letters	Proportion (%) Losing ≥ 15 BCVA Letters	Δ CRT µm Mean	Visits Mean ± SD (Median)	OCT Exams Mean ± SD	Injections Mean ± SD (Range)
Bandukwala et al, 2010 (85)							
All practices	2.88 ± 24.6	25	13	NR	9.4 ± 2.27	3.5 ± 2.66	5.1 ± 2.85
Retinal practice 1	10.7 ± 29.4	NR	NR	NR	8.4 ± 2.21	5.1 ± 2.71	5.0 ± 2.41
Retinal practice 2	−2.9 ± 25.9	NR	NR	NR	8.6 ± 2.99	4.0 ± 2.99	3.3 ± 1.78
Retinal practice 3	5.1 ± 21.8	NR	NR	NR	10.4 ± 2.27	2.7 ± 2.02	6.7 ± 2.77
Carneiro et al, 2012 (86)							
Bevacizumab	5.6	24.8	8.2	−85.3	NR	NR	5.92 ± 2.4
Ranibizumab	6.7	25.0	5.0	−115.2	NR	NR	5.97 ± 2.1
Cohen et al, 2009; (87) 2012 (93)							
Cohort 1	0.7	NR	9.6	NR	NR	NR	3.79 (R,1–7)
Cohort 2	6.97	NR	7.6	NR	NR	NR	4.43 (R, 3–9)
Cohort 3	6.66	NR	4	NR	NR	NR	5.96 (R, 3–10)
Dadgostar et al, 2009 (88)	0.7	30	16	NR	NR	NR	5.2 ± 2.8
Katz et al, 2012 (89)							
Retinal practice 1 (monthly)	13	61	3.2	−151	(13)	NR	(12)
Retinal practice 2 (PRN)	10	38	3.6	−63	(11)	NR	(8)
Kumar et al, 2011 (90)	3.7 ± 10.8	17	2.6	−100 ± 111.9	NR	NR	5.6 ± 2.3
Michalova et al, 2009 (91)	5.5 13.8	NR	7.0	NR	NR	NR	9.2 ± 2.7
Muether et al, 2013 (92)	−0.66 ± 16.82	NR	NR	−115.7	NR	NR	6.9 ± 2.3 (R, 3–11)

Abbreviations: BCVA; best corrected visual acuity; CRT, central retinal thickness; n-AMD, neovascular age-related macular degeneration; NR, not reported; OCT, optical coherence tomography; PRN, pro re nata (as needed); R, range; SD, standard deviation.

The number of re-injections compared with monthly injections was significantly reduced in all studies. The number of visits or the number of OCT investigations performed during the study, although not fixed, was generally not reported. Bandukwala et al (85) were the only investigators to report the number of visits and OCT exams in their follow-up. The relationship between the number of visits and number of OCT exams performed was generally consistent across practices—less than half of the visits had OCT exams performed.

In one retinal practice, the mean number of injections was much higher than the mean number of OCT exams (6.7 vs. 2.7), suggesting that many injections were performed without OCT guidance.

The reduced number of visits, OCT exams, and injections performed in the first year of follow-up was also associated with low VA gains. In general, the mean VA gains at 1-year follow-up reported across the studies were significantly less than those reported in the annual monthly dosing strategies of the landmark MARINA (7.2 letters) and ANCHOR (11.3 letters) trials. The VA gains were also lower than those reported in the PrONTO trial (9.3 letters) with its well prescribed re-treatment protocol and close monitoring and evaluation by OCT. Retinal anatomic measures were not regularly reported in the studies, but when OCT-defined CRT values were reported, improvements were similar to those reported in clinical trials. However, in the Katz et al study, (89) greater improvements in CRT were reported for the cohort receiving monthly reinjections than for the cohort with PRN reinjections (−151 μm vs. −63 μm).

Guidelines

The guidelines from professional national and international societies on follow-up and investigations in patients with retinal diseases being treated with A-VEGF pharmacotherapy are not prescriptive and generally left to the judgment of the treating physician (Table 22). Close monitoring with OCT is, however, recommended by most societies—although details on overall re-treatment strategies and frequency of monitoring intervals are not commented on.

Table 22: Guidelines for Monitoring A-VEGF Treated n-AMD Patients

Society	Year of Recommendation	Guideline
American Academy of Ophthalmology (94)	2008	Follow-up exams (OCT, FA) to be performed as indicated depending on clinical findings and clinical judgment of treating ophthalmologists
International Council of Ophthalmology (95)	2011	After 0.5-mg ranibizumab intravitreal injections, return exam should be approximately 4 weeks after treatment; subsequent follow-up depends on clinical findings and judgment of treating ophthalmologist
Canadian Expert Consensus (24)	2012	Superior VA outcomes in the maintenance phase are achieved with monthly dosing; when not feasible, an individualized regimen with close monitoring by OCT is an option
Italian Retinal Expert Consensus (5)	2012	Use OCT before and after each loading dose, then 1 month after final load. Considering the practical difficulties of monthly monitoring, book monthly checks to 6 months and then every 2 months if no recurrence
European International Retinal Expert Panel (28)	2013	When monthly regimen is impossible, a flexible strategy with monthly monitoring is feasible, but VA benefits might be reduced. A flexible approach requires close monitoring to capture signs of active disease and to re-initiate treatment without delay. Where possible the monthly evaluation should include OCT, the most sensitive means of detecting VEGF-induced permeability changes

Abbreviations: FA, fluorescein angiography; OCT, optical coherence tomography; VA, visual acuity; VEGF, vascular endothelial growth factor.

Discussion

The greatest improvements in vision for n-AMD patients have been with monthly A-VEGF intravitreal injections of ranibizumab or bevacizumab repeated over a 2-year period. The monthly treatment regimen, however, imposes a treatment burden and cost and potentially exposes patients to overtreatment and increased risks. Attempts to reduce treatment burden with other less frequent fixed-dosing schemes, such as fixed quarterly injections, were unsuccessful, resulting in significantly less visual gain with more patients losing vision and fewer improving vision, than those receiving monthly injections.

To individualize treatment for n-AMD patients and tailor treatment to unique relapse patterns, numerous alternate monitoring and PRN treatment strategies have been developed. Strategies in trials that adopted fixed quarterly monitoring visits with PRN-guided re-treatment, however, were also unsuccessful in gaining or stabilizing vision. A PRN strategy of close monthly clinical follow-up with rigorous re-treatment criteria involving VA and OCT imaging for signs of retinal disease progression successfully reduced injection frequency while improving and maintaining vision—similar to VA gains with monthly injections. Monitoring strategies in trials that employed PRN re-treatment criteria guided mainly by clinical signs or VA loss and that did not employ OCT-based criteria were less successful in maintaining or improving vision than PRN strategies involving OCT. The objectives in trials employing OCT-guided PRN re-treatment strategies, however, were focused on the impact of these strategies on reinjection rates and visual outcomes. Follow-up visits and imaging investigations including OCT, therefore, were under protocol involving close follow-up, usually monthly, and actual frequencies of visits or imaging investigations were not reported in major RCTs.

Studies that did evaluate visit and imaging frequency were usually observational cohort studies reporting on the effectiveness of monitoring and PRN re-treatment strategies for n-AMD, under study protocol or as practiced in usual care or real-world settings in many jurisdictions (including Ontario). These studies uniformly reported greatly reduced reinjection frequencies (compared with monthly treatment protocols) similar to the large PRN-guided clinical trials. However, studies on usual care, unlike the major clinical trials, also reported significantly reduced frequencies of visits and OCT-imaging investigations that were associated with more limited visual gains or stabilization in n-AMD patients even in the first follow-up year. Several factors could account for differences in vision outcomes between the clinical trials and usual care. The significantly reduced frequency of both clinical follow-up and OCT exams reported in usual care increases the potential for delayed detection and re-treatment. The broad re-treatment criteria employed in usual care have the potential for inadequate or inappropriate use (including of OCT) and for greater variability in treatment decisions. The main limitation of PRN regimens in practice could be related to logistics and the inability of patients and their physicians to maintain the frequent monthly or bimonthly monitoring visits. It could also be that the broader range of patients treated in usual care included more difficult cases, attenuating the study groups' mean visual gains.

The main disadvantage with PRN re-treatment regimens is that most cases of n-AMD are chronic and require serial injections guided by recurring signs of disease activity that essentially represent failures. A monitoring protocol of waiting and treating after repeated failures potentially risks irreversible retinal damage and vision loss in the long term. Studies evaluating these effects show that initial vision gains do gradually deteriorate over time. Decreasing vision, however, can also be attributed to multiple factors including decreased drug responsiveness or lower retinal resilience, complications related to repeated injections, limited follow-up monitoring, or progression of other untreatable (at this time) AMD components such as GA.

Monotherapy, despite successful PRN-guided re-intervention strategies, has limitations given the multifactorial disease pathways of AMD. Treatment strategies aimed at multiple disease targets employing the adjunct use of lasers with A-VEGF pharmacotherapy have been investigated for more effective or durable treatment outcomes. Increasing the duration of treatment effectiveness, thereby minimizing disease recurrence, could also decrease injections, monitoring visits, and investigations. Although the number of re-interventions was generally reduced in jointly treated patients, the VA gains were generally higher in the A-VEGF monotherapy group. The joint use of lasers and A-VEGF, however, was shown to be more effective for polypoidal choroidal vasculopathy a variant form of n-AMD.

Recently another A-VEGF agent, aflibercept, a different class of A-VEGF pharmacotherapy agent, acting as a soluble decoy with higher VEGF-binding affinity than either ranibizumab or bevacizumab has gained regulatory approval for n-AMD in the United States (FDA, November 2011) and Europe (European Medicines Agency, November 2012) after showing promise as a long-acting anti-angiogenesis intervention. The results achieved in trials under controlled conditions, however, are not always replicated in everyday or usual clinical practice, and the role and broader impact of aflibercept on n-AMD management is currently being evaluated in retinal practices in countries where the drug has regulatory approval.

Conclusions

Significant improvements in vision for n-AMD patients have been achieved with monthly A-VEGF intravitreal injection treatments. Monthly treatment regimens, however, impose a treatment burden and cost and potentially expose patients to overtreatment and increased risks. Since the pivotal trials demonstrating visual improvement with A-VEGF therapy, there has been a greater understanding of the variability in treatment response and disease recurrence among n-AMD patients and that re-treatment regimens tailored to individual disease patterns would be more effective and efficient. Although these re-treatment strategies have been shown to decrease the injection burden while maintaining visual gains, they have been based on close clinical follow-up and a rigorous review of OCT qualitative and quantitative measures of disease activity or recurrence.

Optical coherence tomography–guided PRN treatments have become the preferred and the dominant strategy employed in A-VEGF treatment and follow-up of n-AMD patients in retinal practices. Vision gains reported for A-VEGF PRN treated n-AMD patients in the setting of usual clinical practices in many jurisdictions, however, have been both clinically and statistically significantly lower than those reported in controlled clinical treatment trials. The significantly reduced frequency of visits and imaging investigations reported in usual clinical practice can increase the potential for delayed detection and undertreatment. The less successful PRN treatment in these settings could be related to logistics and the inability of patients and their physicians to maintain the frequent monthly or bimonthly monitoring visits. The infrastructure supports and services available in clinical trials might not be available in clinical practices, limiting monitoring follow-up. The use of long-acting A-VEGF agents such as aflibercept could decrease the need for monthly visits in the first year, but successful PRN-guided re-treatment strategies in subsequent years will continue to depend on close monitoring with tightly defined OCT-guided PRN strategies.

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Appendices

Appendix 1: Literature Search Strategies

Literature search: Optical Coherence Tomography and Retinal Disease: A Rapid Review
Search date: February 7, 2013
Databases searched: Ovid MEDLINE(R) 1946 to January Week 5 2013, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 07, 2013, Embase 1980 to 2013 Week 05

Q: Monitoring strategies with optical coherence (OCT) for patients with retinal diseases (Appropriateness).
Limits: 2008-current; English
Filters: health technology assessments, systematic reviews, and meta-analyses, RCTs

Search Strategy:

#	Searches	Results
1	exp Retinal Diseases/ use mesz	91346
2	exp retina disease/ use emez	164020
3	exp Choroidal Neovascularization/ use mesz	3590
4	exp subretinal neovascularization/ use emez	6130
5	((macul* adj2 (degenerat* or edema*)) or (age-relat* adj2 maculopath*) or choroidal neovascularis* or retinopath* or uveitic maculopath* or central serous retinopath* or epiretinal membrane*).ti,ab.	92977
6	(diabet* adj4 (macul* or retin*)).ti,ab.	37763
7	exp Macular Edema/ use mesz	3669
8	exp Diabetes Mellitus/ use mesz	287906
9	and/7-8	1516
10	or/1-6,9	276766
11	exp Tomography, Optical Coherence/ use mesz	10441
12	exp optical coherence tomography/ use emez	16148
13	(optical coherence adj5 tomograph*).ti,ab.	22967
14	((spectral or fourier) adj2 domain*).ti,ab.	6037
15	(CIRRUS or SPECTRALIS or FD?OCT or 3D OCT?1000 or RTVue or SOCT or OCT?SLO or oct).mp.	35011
16	or/11-15	51117
17	10 and 16	14101
18	Meta Analysis.pt.	36965
19	Meta Analysis/ use emez	68704
20	Systematic Review/ use emez	57019
21	exp Technology Assessment, Biomedical/ use mesz	8791
22	Biomedical Technology Assessment/ use emez	11436
23	(meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.	301636

24	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	3949
25	exp Random Allocation/ use mesz	76124
26	exp Double-Blind Method/ use mesz	117322
27	exp Control Groups/ use mesz	1362
28	exp Placebos/ use mesz	31199
29	Randomized Controlled Trial/ use emez	336510
30	exp Randomization/ use emez	60645
31	exp Random Sample/ use emez	4554
32	Double Blind Procedure/ use emez	112949
33	exp Triple Blind Procedure/ use emez	37
34	exp Control Group/ use emez	41699
35	exp Placebo/ use emez	212212
36	(random* or RCT).ti,ab.	1410151
37	(placebo* or sham*).ti,ab.	454141
38	(control* adj2 clinical trial*).ti,ab.	39002
39	exp Practice Guideline/ use emez	285300
40	exp Professional Standard/ use emez	275062
41	exp Standard of Care/ use mesz	620
42	exp Guideline/ use mesz	23122
43	exp Guidelines as Topic/ use mesz	102366
44	(guideline* or guidance or consensus statement* or standard or standards).ti.	222163
45	(controlled clinical trial or meta analysis or randomized controlled trial).pt.	455842
46	or/18-45	3028958
47	17 and 46	1178
48	limit 47 to english language	1060
49	limit 48 to yr="2008 -Current"	788
50	remove duplicates from 49	535

Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Retinal Diseases] explode all trees	2417
#2	MeSH descriptor: [Choroidal Neovascularization] explode all trees	256
#3	((macul* near/2 (degenerat* or edema*)) or (age-relat* near/2 maculopath*) or choroidal neovascularis* or retinopath* or uveitic maculopath* or central serous retinopath* or epiretinal membrane*):ti (Word variations have been searched)	2226
#4	(diabet* near/2 (macul* or retin*)):ti (Word variations have been searched)	962
#5	MeSH descriptor: [Macular Edema] explode all trees	365
#6	MeSH descriptor: [Diabetes Mellitus] explode all trees	13955
#7	#5 and #6	192
#8	#1 or #2 or #3 or #4 or #7	3479
#9	MeSH descriptor: [Tomography, Optical Coherence] explode all trees	339
#10	(optical coherence near/5 tomograph*):ti (Word variations have been searched)	161
#11	((spectral or fourier) near/2 domain*):ti (Word variations have been searched)	7
#12	(CIRRUS or SPECTRALIS or FD?OCT or 3D OCT?1000 or RTVue or SOCT or OCT?SLO or oct):ti (Word variations have been searched)	741
#13	#9 or #10 or #11 or #12	1107
#14	#8 and #13 from 2008 to 2013	171

Centre for Reviews and Dissemination

Line	Search	Hits
1	MeSH DESCRIPTOR Retinal Diseases EXPLODE ALL TREES	240
2	MeSH DESCRIPTOR Choroidal Neovascularization EXPLODE ALL TREES	35
3	((macul* adj2 (degenerat* or edema*)) or (age-relat* adj2 maculopath*) or choroidal neovascularis* or retinopath* or uveitic maculopath* or central serous retinopath* or epiretinal membrane*):TI	148
4	(diabet* adj2 (macul* or retin*)):TI	51
5	MeSH DESCRIPTOR Choroidal Neovascularization EXPLODE ALL TREES	35
6	MeSH DESCRIPTOR macular edema EXPLODE ALL TREES	26
7	MeSH DESCRIPTOR diabetes mellitus EXPLODE ALL TREES	1443
8	#6 AND #7	16
9	#1 OR #2 OR #3 OR #4 OR #5 OR #8	289
10	MeSH DESCRIPTOR Tomography, Optical Coherence EXPLODE ALL TREES	12

11	(optical coherence adj5 tomograph*):TI	13
12	((spectral or fourier) adj2 domain*):TI	0
13	(CIRRUS or SPECTRALIS or FD?OCT or 3D OCT?1000 or RTVue or SOCT or OCT?SLO or oct)	50
14	#10 OR #11 OR #12 OR #13	59
15	#9 AND #14	9
16	(#15) FROM 2008 TO 2013	5

Appendix 2: GRADE Tables

Table A1: GRADE Evidence Profile for Optical Coherence Tomography–Guided Monitoring for n-AMD

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Visual Outcomes							
Randomized controlled trial	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Not evaluated	None	High
Retinal Anatomic Outcomes							
Randomized controlled trial	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Not evaluated	None	High

Appendix 3: Tables

Table A2: Studies Reviewed in OCT Monitoring Strategies for A-VEGF Treated n-AMD

Authors	Title	Publication
Abraham P, Yue H, Wilson L	Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 2	Am J Ophthalmol. 2010 Sep;150(3):315-24
Antoszyk AN, Tuomi L, Chung CY, Singh A. FOCUS Study Group	Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration (FOCUS): year 2 results	Am J Ophthalmol. 2008 May;145(5):862-74
Bandukwala T, Muni RH, Schwartz C, Eng KT, Kertes PJ	Effectiveness of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration in a Canadian retina practice: A retrospective review	Can J Ophthalmol. 2010;45(6):590-5
Bolz M, Simader C, Ritter M, Ahlers C, Benesch T, Prunte C, et al	Morphological and functional analysis of the loading regimen with intravitreal ranibizumab in neovascular age-related macular degeneration	Br J Ophthalmol. 2010;94(2):185-9
Boyer DS, Heier JS, Brown DM**,** Francom SF, Ianchulev T, Rubio RG	A Phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration	Ophthalmology. 2009;116(9):1731-9
Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al	Ranibizumab versus verteporfin for neovascular age related macular degeneration	N Engl J Med. 2006 Oct 5;355(14):1432
Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T	Ranibizumab versus verteporfin photodynamic therapy for neovascular age related macular degeneration: Two year results of the ANCHOR study	Ophthalmology. 2009 Jan;116(1):57
Carneiro AM, Mendonca LS, Falcao MS, Fonseca SL, Brandao EM, Falcao-Reis FM	Comparative study of 1+PRN ranibizumab versus bevacizumab in the clinical setting	Clin Ophthalmol. 2012;6(1):1149-57
Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, et al	Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial	Ophthalmology. 2012 Jul;119(7):1399-41
Cohen SY, Dubois L, Tadayoni R, Fajnkuchen F, Nghiem-Buffet S, Delahaye-Mazza C, et al	Results of one-year's treatment with ranibizumab for exudative age-related macular degeneration in a clinical setting	Am J Ophthalmol. 2009 Sep;148(3):409-13
Cohen SY, Oubraham H, Uzzan J, Dubois L, Tadayoni R	Causes of unsuccessful ranibizumab treatment in exudative age-related macular degeneration in clinical settings	Retina. 2012 Sep;32(8):1480-5
Dadgostar H, Ventura AA, Chung JY, Sharma S, Kaiser PK	Evaluation of injection frequency and visual acuity outcomes for ranibizumab monotherapy in exudative age-related macular degeneration	Ophthalmology. 2009 Sep;116(9):1740-7
El-Mollayess GM, Mahfoud Z, Schakal AR, Salti HI, Jaafar D, Bashshur ZF	Fixed-interval versus OCT-guided variable dosing of intravitreal bevacizumab in the management of neovascular age-related macular degeneration: a 12-month randomized prospective study	Am J Ophthalmol. 2012;153(3):481-9
Ernst BJ, Barkmeier AJ, Akduman L	Optical coherence tomography-based intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration	Int Ophthalmol. 2010 Jun;30(3):267-70
Fung AE, Lalwani GA, Rosenfeld PJ, Dubovy SR, Michels S, Feuer WJ, et al	An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration	Am J Ophthalmol. 2007 Apr;143(4):566-83
Fung AT, Kumar N, Vance SK, Slakter JS, Klancnik JM, Spaide RS, et al	Pilot study to evaluate the role of high-dose ranibizumab 2.0 mg in the management of neovascular age-related macular degeneration in patients with persistent/recurrent macular fluid <30 days following treatment with intravitreal anti-VEGF therapy (the LAST Study)	Eye. 2012;26:1181-7
Gerding H, Loukopoulos V, Riese J, Hefner L, Timmermann M	Results of flexible ranibizumab treatment in age-related macular degeneration and search for parameters with impact on outcome	Graefes Arch Clin Exp Ophthalmol. 2011 May;249(5):653-62

Authors	Title	Publication
Heier JS, Boyer DS, Ciulla TA, Ferrone PJ, Jumper JM, Gentile RC, et al	Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration: year 1 results of the FOCUS Study	Arch Ophthalmol. 2006 Nov;124(11):1532-42
Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, et al	Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration	Ophthalmology. 2012 Dec;119(12):2537-48
Heimes B, Lommatzsch A, Zeimer M, Gutfleisch M, Spital G, Dietzel M, et al	Long-term visual course after anti-VEGF therapy for exudative AMD in clinical practice evaluation of the German reinjection scheme	Graefes Arch Clin Exp Ophthalmol. 2011 May;249(5):639-44
Holz FG, Amoaku W, Donate J, Guymer RH, Kellner U, Schlingemann RO, et al	Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: The SUSTAIN study	Ophthalmology. 2011;118(4):663-71
Kaiser PK, Boyer DS, Cruess AF, Slakter JS, Pilz S, Weisberger A	Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study	Ophthalmology. 2012 May;119(5):1001-10
Kang S, Roh YJ	One-year results of intravitreal ranibizumab for neovascular age-related macular degeneration and clinical responses of various subgroups	Jpn J Ophthalmol. 2009 Jul;53(4):389-95
Katz G, Giavedoni L, Muni R, Evans T, Pezda M, Wong D, et al	Effectiveness at 1 year of monthly versus variable-dosing intravitreal ranibizumab in the treatment of choroidal neovascularization secondary to age-related macular degeneration	Retina. 2012;32(2):293-8
Krebs I, Vecsei M, V, Bodenstorfer J, Glittenberg C, Ansari SS, Ristl R, et al	Comparison of Ranibizumab monotherapy versus combination of ranibizumab with photodynamic therapy with neovascular age-related macular degeneration	Acta Ophthalmol. 2013 May;91(3):e178-e183
Krebs I, Schmetterer L, Boltz A, Told R, Vecsei-Marlovits V, Egger S, et al	A randomised double-masked trial comparing the visual outcome after treatment with ranibizumab or bevacizumab in patients with neovascular age-related macular degeneration.	Br J Ophthalmol. 2013 Mar;97(3):266-71
Kruger FM, Kemp H, Sorensen TL	Four-year treatment results of neovascular age-related macular degeneration with ranibizumab and causes for discontinuation of treatment	Am J Ophthalmol. 2013 Jan;155(1):89-95
Kumar A, Sahni JN, Stangos AN, Campa C, Harding SP	Effectiveness of ranibizumab for neovascular age-related macular degeneration using clinician-determined re-treatment strategy	Br J Ophthalmol. 2011;95(4):530-3
Lalwani GA, Rosenfeld PJ, Fung AE, Dubovy SR, Michels S, Feuer W, et al	A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study	J Ophthalmol. 2009 Jul;148(1):43-58
Larsen M, Schmidt-Erfurth U, Lanzetta P, Wolf S, Simader C, Tokaji E, et al	Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results	Ophthalmology. 2012 May;119(5):992-1000
Li X, Hu Y, Sun X, Zhang J, Zhang M, Neovascular Age-Related Macular Degeneration Treatment Trial Using Bevacizumab (NATTB)	Bevacizumab for neovascular age-related macular degeneration in China	Ophthalmology. 2012;119(10):2087-93
Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ	Ranibizumab and bevacizumab for neovascular age-related macular degeneration	N Engl J Med. 2011 May 19;364(20):1897-908
Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, et al	Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results	Ophthalmology. 2012 Jul;119(7):1388-98
Michalova K, Wickremasinghe SS, Tan TH, Chang A, Harper CA, Downie JA, et al	Ranibizumab treatment for neovascular age-related macular degeneration: from randomized trials to clinical practice	Eye. 2009 Aug;23(8):1633-40
Muether PS, Hoerster R, Hermann MM, Kirchhof B, Fauser S	Long-term effects of ranibizumab treatment delay in neovascular age-related macular degeneration	Graefes Arch Clin Exp Ophthalmol. 2013 Feb;251(2):453-8

Authors	Title	Publication
Muniraju R, Ramu J, Sivaprasad S	Three-year visual outcome and Injection frequency of intravitreal ranibizumab therapy for neovascular age-related macular degeneration	Ophthalmologica. 2013 Apr 30;230(1):27-33
Oubraham H, Cohen SY, Samimi S, Marotte D, Bouzaher I, Bonicel P, et al	Inject and extend dosing versus dosing as needed: a comparative retrospective study of ranibizumab in exudative age-related macular degeneration	Retina. 2011 Jan;31(1):26-30
Regillo CD, Brown DM, Abraham P, Yue H, Ianchulev T, Schneider S, et al	Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1	Am J Ophthalmol. 2008 Feb;145(2):239-48
Rothenbuehler SP, Waeber D, Brinkmann CK, Wolf S, Wolf-Schnurrbusch UE	Effects of ranibizumab in patients with subfoveal choroidal neovascularization attributable to age-related macular degeneration	Am J Ophthalmol. 2009 May;147(5):831-7
Rudnisky CJ, Liu C, Ng M, Weis E, Tennant MT	Intravitreal bevacizumab alone versus combined verteporfin photodynamic therapy and intravitreal bevacizumab for choroidal neovascularization in age-related macular degeneration: visual acuity after 1 year of follow-up	Retina. 2010 Apr;30(4):548-54
Schmidt-Erfurth U, Eldem B, Guymer R, Korobelnik JF, Schlingemann RO, Axer-Siegel R, et al	Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study	Ophthalmology. 2011;118(5):831-9
Silva R, Axer-Siegel R, Eldem B, Guymer R, Kirchhof B, Papp A, et al	The SECURE study: long-term safety of ranibizumab 0.5 mg in neovascular age-related macular degeneration	Ophthalmology. 2013 Jan;120(1):130-9
Singer MA, Awh CC, Sadda S, Freeman WR, Antoszyk AN, Wong P, et al	HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration	Ophthalmology. 2012 Jun;119(6):1175-83
Soderberg A-C, Algvere PV, Hengstler JC, Soderberg P, Seregard S, Kvanta A	Combination therapy with low-dose transpupillary thermotherapy and intravitreal ranibizumab for neovascular age-related macular degeneration: A 24-month prospective randomised clinical study	Br J Ophthalmol. 2012;96(5):714-8
Subramanian ML, Abedi G, Ness S, Ahmed E, Fenberg M, Daly MK, et al	Bevacizumab vs ranibizumab for age-related macular degeneration: 1-year outcomes of a prospective, double-masked randomised clinical trial	Eye. 2010;24(11):1708-15
Williams PD, Callanan D, Solley W, Avery RL, Pieramici DJ, Aaberg T	A prospective pilot study comparing combined intravitreal ranibizumab and half-fluence photodynamic therapy with ranibizumab monotherapy in the treatment of neovascular age-related macular degeneration	Clin Ophthalmol. 2012;6(1):1519-25
Ying G-S, Huang J, Maguire MG, Jaffe GJ, Grunwald JE, Toth C, et al	Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration	Ophthalmology. 2013;120(1):122-9

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