

Alternative anti-VEGF treatment regimens in exudative age-related macular degeneration

Expert Rev. Ophthalmol. 5(6), 799–809 (2010)

Robert B Bhisitkul¹
and Jay M Stewart¹

¹Beckman Vision Center, University of California San Francisco, 10 Koret Way, K301, San Francisco, CA 94143, USA
*Author for correspondence:
Tel.: +1 415 476 8633
bhisitkulr@vision.ucsf.edu

This article evaluates the currently used treatment regimens in ocular anti-VEGF therapy for exudative age-related macular degeneration. Anti-VEGF therapies using variable injection regimens and combination therapies have emerged as alternatives to standard monthly monotherapy to address drug costs, patient risks and indisposition, and office workload. Variable anti-VEGF regimens employ reduced-frequency intravitreal injections on an as-needed basis or a fixed intermittent schedule. Although high-level evidence available from randomized clinical trials generally indicates less favorable outcomes for variable anti-VEGF regimens, positive results from some prospective and retrospective studies support variable therapies. Combination anti-VEGF therapies most often incorporate verteporfin photodynamic therapy and/or intravitreal corticosteroids. High-level evidence is not yet published for combination therapies, but therapeutic success with reduced treatments has been reported in uncontrolled and retrospective studies. Evidence to establish relative efficacy will be derived from ongoing randomized clinical trials comparing alternative regimens to standard monthly anti-VEGF monotherapy.

KEYWORDS: age-related macular degeneration • bevacizumab • intravitreal corticosteroids • intravitreal injection • photodynamic therapy • ranibizumab

Since intravitreal anti-VEGF agents became available for the treatment of exudative age-related macular degeneration (AMD), ophthalmologists have been reconsidering standard monthly dosing strategies and exploring alternative treatment approaches with these agents. These alternative anti-VEGF regimens can be broadly classified as:

- Variable-dosing regimens, defined here as anti-VEGF monotherapies using intravitreal injections less frequently than once a month and usually for less than 1–2 years' duration;
- Combination therapies, employing anti-VEGF agents in conjunction with other AMD treatment modalities, in particular verteporfin photodynamic therapy (PDT) and/or intravitreal corticosteroids.

Treating physicians have several objectives when employing these alternative therapeutic regimens:

- Foremost, to decrease the number and frequency of intravitreal injections, thereby reducing ocular risks (and theoretical systemic risks), drug and procedural costs, patient discomfort and indisposition, and office workload and resources;
- To allow discontinuation of treatment upon cessation of disease activity, thereby attaining a therapeutic end point;
- To seek improved visual outcomes relative to standard therapy by combining different therapies with distinct targets of action, and potentially achieving additive or synergistic effects.

The use of alternative dosing regimens has been predicated on the clinical perception that their therapeutic benefits are equivalent to those achieved with standard monthly ranibizumab treatment as established in the MARINA and ANCHOR trials [1–3]. The answer to the question

of relative therapeutic efficacy awaits completion of ongoing randomized clinical trials of these alternative regimens. In this article, we evaluate the relative efficacy of current alternative anti-VEGF treatment regimens in neovascular AMD on the basis of available preclinical and clinical evidence, and ongoing clinical trials.

Current therapies in exudative AMD

Approved & off-label therapies

Currently, five pharmacologic therapies are used to treat exudative AMD (FIGURE 1). Three therapies are approved by the US FDA for this indication: verteporfin PDT [4,5], pegaptanib sodium (Macugen®; OSI/Eyetech Pharmaceuticals, NY, USA) [6,7] and ranibizumab (Lucentis®; Genentech, Inc., CA, USA) [1,3,8]. Intravitreal bevacizumab (Avastin®; Genentech, Inc.) and triamcinolone acetonide (and other injectable corticosteroids) are also widely used off-label for the treatment of exudative AMD.

Ranibizumab, PDT and pegaptanib have been shown in large, randomized clinical trials to be safe and effective in the treatment of patients with exudative AMD [1,3,4,9]. Currently, ranibizumab

and bevacizumab are the most widely used in neovascular AMD. Ranibizumab is an intravitreally injected humanized anti-VEGF-A antibody fragment that binds all VEGF-A isoforms and their biologically active degradation products [10]. Bevacizumab, derived from the same parent molecule as ranibizumab, is a humanized anti-VEGF-A antibody that also binds all VEGF-A isoforms and their biologically active degradation products [11]. Although bevacizumab is FDA approved only for intravenous use in combination with chemotherapy for the treatment of colorectal, breast, lung and renal cell cancers, clinical experience with intravitreal bevacizumab has shown that this agent is well tolerated and associated with improved vision and decreased retinal thickness in patients with exudative AMD [12–15]. Given its substantially lower cost than ranibizumab, bevacizumab has gained increasing popularity as an off-label AMD treatment.

Therapies in development

In addition to the aforementioned therapies currently in use, several therapies are in clinical development for the treatment

of exudative AMD, including the 'decoy receptor' VEGF Trap-Eye (Regeneron, NY, USA), the radioisotope Epi-Rad90™ Ophthalmic System (NeoVista, Inc., CA, USA), siRNAs such as bevasiranib (Cand5; OPKO Health, Inc., FL, USA) and Sirna-027 (Sirna Therapeutics, CO, USA), the PDGF-targeted aptamer E10030 (Ophthotech Corp., NJ, USA). Many of these emerging agents are being investigated as some form of combination therapy in their development strategy, either as an adjunctive therapy (integrated with anti-VEGF drugs) or as a follow-on (maintenance) treatment after initial ranibizumab treatment. Alternative regimens using drugs in development will not be discussed further in this article.

Rationale for variable-dosing regimens

In clinical practice today, few retinal specialists adhere to the strict schedule of regular monthly intravitreal injections for 2 years as established by the MARINA and ANCHOR trials. A variety of variable treatment strategies have arisen, most of which utilize an initial series of several monthly injections followed by intermittent injections on either a fixed intermittent schedule (e.g., every 3 months) or on a *pro re nata* (PRN) basis. Although drug cost is a prime consideration in reducing dosing frequency, variable treatment approaches prevail even with the use of the lower cost agent, bevacizumab.

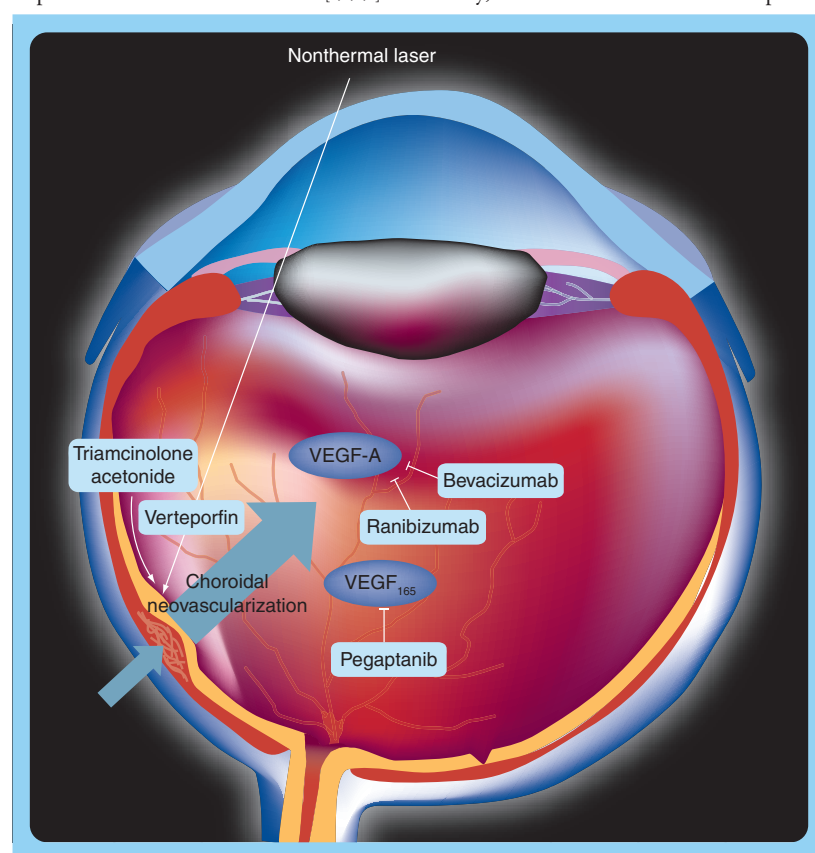


Figure 1. Mechanisms of action of current therapies in exudative age-related macular degeneration. Currently, five therapies are used in the treatment of exudative age-related macular degeneration, including verteporfin photodynamic therapy, the anti-VEGF aptamer pegaptanib sodium, which targets VEGF₁₆₅, and the anti-VEGF monoclonal antibody fragment ranibizumab, which targets all isoforms of VEGF-A and its degradation products. Therapies used off-label include the corticosteroid triamcinolone acetonide and the anti-VEGF humanized monoclonal antibody bevacizumab.

The primary scientific rationale for variable therapy is to avoid treatment when it is not considered necessary, as when the macula has become clinically dry after treatment. Reducing the frequency of injections while achieving equivalent outcomes aims to maximize the therapeutic efficiency. In PRN regimens, the clinician performs ongoing follow-up to reinstate therapy upon the reappearance of exudation; thus, these approaches rely on the reversibility of episodic visual declines during the course of treatment. Individualized treatment is another rationale for variable therapy, emphasizing the physician's clinical judgment in the management of each patient, rather than rote retreatment on a monthly basis.

On the other hand, the scientific rationale for standard continuous monthly therapy is based on VEGF biology, drug pharmacokinetics, and available Phase III clinical trial data. VEGF is continuously expressed in the retina and retinal pigment epithelium (RPE) in normal adult nonhuman primates and rodents [16], with increased VEGF levels in choroidal neovascularization (CNV) membranes [17,18]. In humans, inferential evidence suggests that VEGF activity is sustained in exudative AMD; even chronic CNV membranes surgically removed from exudative AMD patients show strong VEGF labeling [19]. Furthermore, patients in the control arms of randomized clinical trials of anti-VEGF treatment for exudative AMD showed progressive visual decline for 2 or more years, again suggesting a role for chronic VEGF activity in the natural course of the disease [3,4,9].

Monthly dosing has also been guided by the pharmacokinetics of ranibizumab and bevacizumab, both large-molecule biologics that are rapidly degraded and cleared from the eye. In the vitreous of rabbits and nonhuman primates, 0.5 mg of ranibizumab has a half-life of 2.9 and 2.6 days, respectively [20,21]. In human eyes, measurements of ranibizumab concentrations following intravitreal injection are consistent with a half-life of approximately 3 days, with clearance below effective concentrations at 4 weeks [22]. For bevacizumab, pharmacokinetic data show a vitreous half-life of approximately 4 days in rabbit eyes [23] and 6.7 days in human eyes [24].

Clinical trial evidence

Standard dosing

MARINA and ANCHOR, two pivotal Phase III multicenter randomized, controlled clinical trials of intravitreal ranibizumab monotherapy, have established and quantified the therapeutic benefit associated with the continuous monthly injection regimen (TABLE 1). In both the MARINA trial of 716 patients with minimally classic and occult CNV [3] and the ANCHOR trial of 423 patients with predominantly classic CNV [1], patients assigned to the ranibizumab treatment arms received monthly intravitreal injections (0.3 or 0.5 mg) for 2 years for a mean number of 21.9 and 21.4 injections per patient, respectively. At 12 months, patients in MARINA had a mean increase in visual acuity (VA) of 6.5 and 7.2 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in the 0.3 and 0.5 mg ranibizumab cohorts, respectively, compared with a mean decrease of 10.4 letters in the sham cohort. In ANCHOR, at 12 months patients

had a mean increase in VA of 8.5 and 11.3 letters in the 0.3 and 0.5 mg ranibizumab cohorts, respectively, compared with a mean decrease of 9.5 letters in the PDT cohort. In both MARINA and ANCHOR, visual function improvement was sustained through 24 months: at this time point, patients in MARINA had mean increases in VA of 5.4 and 6.6 letters in the 0.3 and 0.5 mg ranibizumab cohorts, respectively, compared with a decrease of 14.9 letters in the sham cohort. Patients in ANCHOR achieved a mean increase in VA of 8.1 and 10.7 letters in the 0.3 and 0.5 mg ranibizumab cohorts, respectively, compared with a decrease of 9.8 letters in patients receiving verteporfin PDT.

Variable dosing

Six clinical studies (A Study of rhuFAB V2 [Ranibizumab] in Subjects with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration [PIER], Prospective Optical Coherence Tomography Imaging of Patients With Neovascular AMD Treated With Intra-Ocular Ranibizumab [Lucentis] [PrONTO], 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 [HORIZON], A Study to Evaluate Ranibizumab in Subjects With Choroidal Neovascularization [CNV] Secondary to Age-Related Macular Degeneration [SAILOR], Efficacy and Safety of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration [EXCITE], and Study of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration [SUSTAIN]) have evaluated the safety and efficacy of variable dosing of ranibizumab monotherapy (TABLE 1). Whereas the PIER and EXCITE studies used a variable regimen of fixed dosing intervals, the PrONTO, HORIZON, SUSTAIN and SAILOR studies used a PRN regimen (each with different protocols and retreatment criteria).

PIER was a Phase IIIb multicenter, double-masked, sham injection-controlled trial using a fixed variable injection protocol, in which AMD patients ($n = 184$) with predominantly or minimally classic, or occult (with no classic), CNV lesions were randomized to receive intravitreal ranibizumab (0.3 or 0.5 mg) or sham injections monthly for the first 3 months, followed by injections every 3 months [8]. This alternative dosing regimen was selected based on earlier Phase I and II studies showing that the clinical effect of ranibizumab (0.3 and 0.5 mg) may last for 90 days [25,26]. During the initial monthly injection phase, patients receiving ranibizumab showed a mean improvement in VA by the third month; however, in the subsequent phase of fixed quarterly injections, the mean VA declined to less than baseline VA at 12 months so that the overall mean change in VA was a decrease of 1.6 and 0.2 letters in the 0.3 and 0.5 mg ranibizumab cohorts, respectively, compared with a loss of 16.3 letters in the sham-injected cohort ($p \leq 0.0001$). Although VA outcomes were statistically better with ranibizumab than with control injections, the visual outcomes were not as robust as those reported with continuous monthly ranibizumab therapy in the MARINA and ANCHOR trials.

Table 1. Summary of presented/published clinical trials of ranibizumab standard monthly and variable dosing regimens for exudative age-related macular degeneration.

Dosing regimen	Trial acronym/ name	Phase/design	Patients (n)	Mean treatments per year (n)	Follow- up (months)	Outcomes (from baseline)		Ref.
						Mean change in VA (letters) (%)	≥3-line gain <3-line loss (%)	
Monthly	ANCHOR	Phase III, randomized, multicenter, double masked, sham controlled, 1:1:1 (0.3 mg Ran:0.5 mg Ran:PDT)	423	12 [†]	12	0.3 mg: +8.5; 0.5 mg: +11.3; PDT: -9.5	0.3 mg: 35.7; 0.5 mg: 40.3; PDT: 5.6	[2]
					24	0.3 mg: +8.1; 0.5 mg: +10.7; PDT: -9.8	0.3 mg: 34.3; 0.5 mg: 41.0; PDT: 6.3	[1]
Monthly	MARINA	Phase III, randomized, multicenter, double masked, sham controlled, 1:1:1 (0.3 mg Ran:0.5 mg Ran:sham)	716	12 [†]	12	0.3 mg: +6.5; 0.5 mg: +7.2; sham: -10.4	0.3 mg: 24.8; 0.5 mg: 33.8; sham: 5.0	[3]
					24	0.3 mg: +5.4; 0.5 mg: +6.6; sham: -14.9	0.3 mg: 26.1; 0.5 mg: 33.3; sham: 3.8	
Variable, PRN	PRONTO	Phase I/II, nonrandomized, single center (0.5 mg Ran)	40	5.6	12	0.5 mg: +9.3	0.5 mg: 35	[27,28]
Variable, quarterly	PIER	Phase III, randomized, multicenter, double masked, sham controlled, 1:1:1 (0.3 mg Ran:0.5 mg Ran:sham)	184	6	12	0.3 mg: -1.6; 0.5 mg: -0.2; sham: -16.3	0.3 mg: 11.7; 0.5 mg: 13.1; sham: 9.5	[8]
Variable, PRN	HORIZON	Phase III, multicenter, extension (0.5 mg Ran)	853	NA	12	NA	T: 2.0; XO: 3.0; N: 2.0	[30,101]
Variable, PRN	SAILOR (cohort 1)	Phase III, randomized, multicenter, single masked, 1:1 (0.3 mg Ran:0.5 mg Ran)	2378	NA	12	0.3 mg N: +0.5; 0.5 mg N: +2.3; 0.3 mg T: 15.8; 0.3 mg T: +1.7; 0.5 mg T: +2.3	0.3 mg N: 14.6; 0.5 mg N: 19.3; 0.3 mg T: 15.8; 0.5 mg T: 16.5	[29,102]
Variable, quarterly	EXCITE	Phase III, controlled 1:1:1 (0.3 mg Ran quarterly: 0.5 mg Ran quarterly: 0.3 mg Ran monthly)	353	NA	12	NA	NA	[31,103]
Variable, PRN	SUSTAIN	Phase III, open label (0.3 mg Ran)	513	NA	12	NA	NA	[32,104]

[†]Theoretical mean number of injections per year based on monthly dosing regimen.

AAO: American Academy of Ophthalmology; AMD: Age-related macular degeneration; ARVO: Association for Research in Vision and Ophthalmology; EXCITE: Efficacy and Safety of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration; 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; N: Not treated; NA: Not applicable; PDT: Photodynamic therapy; PIER: A Study of rhuFAB V2 (Ranibizumab) in Subjects with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration; PRN: *Pro re nata*; PRONTO: Prospective Optical Coherence Tomography Imaging of Patients With Neovascular AMD Treated With Intra-Ocular Ranibizumab (Lucentis); Ran: Ranibizumab; RS: Retina Society; SAILOR: A Study to Evaluate Ranibizumab in Subjects With Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration; SUSTAIN: Study of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration; T: Previously treated; XO: Crossover.

The results of the investigator-sponsored PrONTO study, a Phase I/II prospective, open-label 2-year trial (n = 40 patients), have had a strong influence on the widespread adoption of variable-dosing regimens in clinical practice [27]. The PrONTO regimen consisted of 3-monthly ranibizumab (0.5 mg) injections followed by selective dosing at monthly follow-up visits. Retreatment criteria were strict, including VA loss of five or more letters with evidence from optical coherence tomography of new macular fluid or persistent fluid following the last injection; an increase in central retinal thickness (CRT) of 100 μ m or more; or new macular hemorrhage. Criteria during the second year were strengthened to include retreatment for any subjective evidence of macular fluid. Outcomes were favorable; 1-year data demonstrated that the PrONTO regimen reduced the number of injections to an average of 5.6 during the first year, with a mean improvement from baseline VA of 9.3 letters. At 2 years, the mean number of total injections was 9.9, with a mean visual improvement of 11.1 letters [27,28].

The SAILOR study, the largest trial in exudative AMD to date (n = 4307), was a Phase IIIb multicenter, 1-year study evaluating a variable-dosing regimen of 3-monthly intravitreal ranibizumab (0.3 or 0.5 mg) injections followed by PRN dosing in two patient cohorts. Follow-up visits were required every 3 months, and retreatment criteria included a VA loss of more than five letters compared with the patient's peak VA, or an increase in CRT (as measured by optical coherence tomography) of more than 100 μ m with intraretinal or subretinal fluid, relative to the patient's best earlier measurements. Within the randomized, single-masked cohort 1 (n = 2378) at 1-year follow-up, treatment-naïve patients experienced mean VA improvements of 0.5 and 2.3 letters in the 0.3 and 0.5 mg groups, respectively, while previously treated patients experienced mean VA improvements of 1.7 and 2.3, respectively [29]. The visual outcomes achieved with the variable PRN regimen in the SAILOR trial compare unfavorably with those reported in the MARINA and ANCHOR trials, in which continuous monthly therapy was used. Moreover, the visual outcomes in SAILOR also compare unfavorably with those of the PrONTO study, although the studies differed with respect to the variable regimens and retreatment criteria employed.

The HORIZON study, although designed as an extension study, provides another assessment of the efficacy of variable therapy. HORIZON was a Phase III open-label extension trial for patients who completed 2 years of ranibizumab or control treatment in the Phase III ANCHOR and MARINA trials, or the Phase I/II Intravitreal Injections of rhuFab V2 in Combination With Visudyne in Subjects

With Age-Related Macular Degeneration (FOCUS) trial (discussed in 'Combination therapies' section) [30]. On entering into HORIZON, patients were switched to a PRN regimen (dosing no more frequently than every 30 days) based on the discretion of the treating physician, with required patient visits every 3 months. Of 853 patients enrolled into HORIZON, 600 comprised the 'treated cohort' and had been in study groups previously treated with monthly ranibizumab injections. The remaining patients had previously received PDT or sham injections and were either in the ranibizumab crossover cohort (n = 168) or did not require further treatment (n = 85). Patients in the treated cohort showed a mean VA loss of 5.3 letters from study baseline, a reversal of the mean VA gains achieved (+9.4 letters) with their previous monthly treatments within the MARINA, ANCHOR and FOCUS trials. Patients in the crossover and untreated cohorts experienced a mean VA loss of 2.4 and 3.1 letters, respectively, from study baseline.

A comparison of mean changes in VA over 12 months for patients receiving 0.5 mg of ranibizumab as standard therapy or variable therapy is illustrated in Figure 2, although this should be interpreted with caution in light of the limitations of cross-trial comparisons.

The EXCITE study was a Phase IIIb, multicenter, active-controlled, double-masked clinical trial in which patients were randomized to 3-monthly loading doses of 0.3 or 0.5 mg ranibizumab followed by quarterly injections or 0.3 mg monthly injections through 12 months follow-up. Although data from the monthly dosing group have not yet been published, preliminary data suggest some clinical benefit of quarterly dosing through 12 months [31]. Similarly, preliminary data from the SUSTAIN trial (a Phase IIIb,

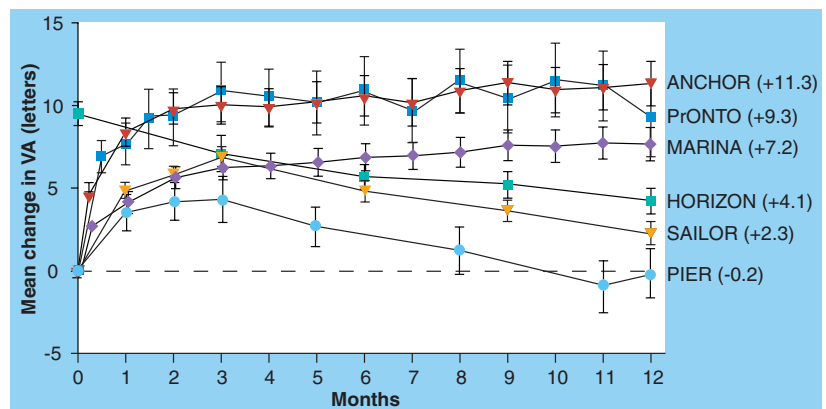


Figure 2. Visual acuity changes with ranibizumab. Mean change in Early Treatment Diabetic Retinopathy Study (ETDRS) letters through 12-month follow-up with 0.5 mg ranibizumab for monthly (ANCHOR, MARINA) and variable-dosing regimens (HORIZON [treated cohort], SAILOR [cohort 1], PIER and PrONTO). HORIZON: 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; PIER: A Study of rhuFAB V2 (Ranibizumab) in Subjects with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration; PrONTO: Prospective Optical Coherence Tomography Imaging of Patients With Neovascular AMD Treated With Intra-Ocular Ranibizumab (Lucentis); SAILOR: A Study to Evaluate Ranibizumab in Subjects With Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration; VA: Visual acuity.

multicenter, open-label, single-arm clinical trial) in which patients received 3-monthly loading doses of 0.3 mg ranibizumab followed by PRN doses guided by changes in VA and CRT, have shown some clinical benefit of a PRN dosing regimen through 12 months [32].

The therapeutic benefits of standard monthly therapy versus variable treatment will be compared directly in upcoming large, randomized clinical trials. In the Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) study, currently enrolling 1200 patients, attention is focused on comparisons of bevacizumab and ranibizumab monotherapy. However, study arms in CATT will also allow for head-to-head comparisons of visual outcomes with standard monthly and variable regimens. Other head-to-head trials of bevacizumab compared with ranibizumab monotherapy under a monthly or variable dosing regimen are presented in TABLE 2.

Combination therapies

Rationale

The clinical use of combination therapies is well established in other areas of medicine such as infectious disease and oncology. Since available treatments for exudative AMD have distinct mechanisms of action, combining these agents may provide synergistic or additive effects (FIGURE 1), which may translate into visual benefits superior to those achieved with anti-VEGF monotherapy. As an example, adjuvant anti-VEGF therapy could offset the increased VEGF expression that has been reported with verteporfin PDT therapy [33].

Individualized treatment is also a rationale for combination therapies; a patient's incomplete response to any single treatment can be addressed by switching to or adding other modalities. Cessation of CNV activity, with the possibility of permanent disease quiescence, is another goal of combination therapy. Furthermore, as with variable treatment

monotherapies, combination therapies are aimed at reducing treatment frequency and attendant risks, financial costs and clinician workload.

The data from evidence-based comparisons of anti-VEGF monotherapies versus combination therapies are limited at present. Data describing combination therapy with ocular anti-VEGF agents plus verteporfin PDT and/or intraocular corticosteroids have largely been reported as retrospective case series or small uncontrolled studies. Results are expected from clinical trials of various combination therapies for bevacizumab (TABLE 2) and ranibizumab (TABLE 3).

PDT plus anti-VEGF therapy

FOCUS was a Phase I/II multicenter, 2-year, randomized, single-masked, controlled study in which patients (n = 162) received PDT in combination with monthly intravitreal ranibizumab (0.5 mg) or sham injections. PDT was performed 7 days before initial ranibizumab or sham treatment and then quarterly as needed (standard of care at the time) [34,35]. At the 24-month follow-up, patients treated with ranibizumab plus PDT achieved a mean increase in VA of 4.6 letters compared with patients receiving sham injections plus PDT, who experienced a mean decrease in VA of 7.8 letters [35].

In case series and uncontrolled studies, combination therapy of verteporfin PDT with intravitreal bevacizumab has been reported to improve mean VA and reduce central macular thickness in patients with exudative AMD while also reducing retreatment rates [36–38]. Randomized studies providing a direct comparison of anti-VEGF monotherapy to PDT-based combination therapy are forthcoming. The ongoing Verteporfin Photodynamic Therapy Administered in Conjunction with Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (DENALI) and Efficacy/Safety

Table 2. Summary of ongoing Phase III clinical trials of bevacizumab in exudative age-related macular degeneration.

Dosing regimen	Trial acronym/ name	Design	Patients (n)	Follow-up (months)	Ref.
Monotherapy (monthly/variable)	CATT	Randomized, multicenter, double-masked, controlled (Bev vs Ran)	1208	24	[105]
Monotherapy (monthly/variable)	IVAN	Randomized, multicenter, double-masked, controlled (Bev vs Ran)	600 [†]	24	[106]
Monotherapy (monthly/variable)	MANTA	Randomized, multicenter, double-masked, controlled (Bev vs Ran)	320 [†]	12	[107]
Monotherapy (monthly/variable)	VIBERA	Randomized, multicenter, double-masked, controlled (Bev vs Ran)	366 [†]	24	[108]
Combination	NA	Randomized, single center, single-masked, controlled (Bev + PDT vs Bev + PDT + triamcinolone)	NA	NA	[109]

[†]Estimated patient enrollment.

AMD: Age-related macular degeneration; Bev: Bevacizumab; CATT: Comparison of Age-Related Macular Degeneration Treatment Trials; IVAN: A Randomized Controlled Trial of Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularization; MANTA: Avastin Versus Lucentis in Age-Related Macular Degeneration; NA: Not available; PDT: Photodynamic therapy; Ran: Ranibizumab; VIBERA: Prevention of Vision Loss in Patients With Age-Related Macular Degeneration (AMD) by Intravitreal Injection of Bevacizumab and Ranibizumab.

Table 3. Summary of published and ongoing clinical trials of ranibizumab combination therapy in exudative age-related macular degeneration.

Dosing regimen	Trial acronym/name	Phase/design	Patients (n)	Mean treatments per year (n)	Follow-up (months)	Outcomes (from baseline)			Ref.
						Mean change in VA (letters)	≥3-line gain (%)	<3-line loss (%)	
Monthly/standard	FOCUS	Phase I/II, randomized, single masked, 2:1 (0.5 mg Ran + PDT vs sham + PDT)	162	12 [†]	24	Ran + PDT: 4.6; sham + PDT: -7.8	Ran + PDT: 25; sham + PDT: 7	Ran + PDT: 88; sham + PDT: 75	[35]
Monthly/variable	MONT BLANC	Phase II/III, randomized, multicenter, double masked, controlled (0.5 mg Ran + PDT vs Ran)	323	NA	24	NA	NA	NA	[110]
Monthly/variable	DENALI	Phase II/III, randomized, multicenter, double masked, controlled (0.5 mg Ran + PDT vs Ran)	255	NA	24	NA	NA	NA	[111]
Monthly/standard	CARBON	Phase III, randomized, multicenter, double masked, controlled (Ran + Bs vs Ran)	496	12 [†]	~15	NA	NA	NA	[112]
Variable	CABERNET	Phase III, randomized, multicenter, controlled (0.5 mg Ran + EpiRad90)	450	NA	12	NA	NA	NA	[113]
Combination vs monotherapy	LuceDex	Phase I/II prospective (Ran + Dex vs Ran)	40	NA	12	NA	NA	NA	[114]
Triple therapy vs monotherapy	RADICAL	Phase II, randomized, multicenter, controlled (Ran + PDT vs Ran + PDT + Dex vs Ran)	160	NA	12	NA	NA	NA	[115]
Triple therapy vs monotherapy	PDEX	Phase II randomized, single masked (PDT + Dex + Ran vs Ran)	60	NA	12	NA	NA	NA	[116]

[†]Theoretical mean number of injections per year based on monthly dosing regimen.
Bs: Bevasiranib sodium; CABERNET: A study of Strontium⁹⁰ β Radiation With Lucentis to Treat Age-Related Macular Degeneration; CARBON: Combination of Bevasiranib and Lucentis Therapy in Wet AMD; DENALI: Verteporfin Photodynamic Therapy Administered in Conjunction with Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration; Dex: Dexamethasone; FOCUS: Phase I/II Intravitreal Injections of rhuFab V2 in Combination with Visudyne in Subjects with Age-Related Macular Degeneration; LuceDex: A Prospective Study Comparing Ranibizumab Plus Dexamethasone Combination Therapy Versus Ranibizumab Monotherapy for Wet AMD; MONT BLANC: Efficacy/Safety of Verteporfin Photodynamic Therapy and Ranibizumab Compared with Ranibizumab in Patients with Subfoveal Choroidal Neovascularization; NA: Not applicable; PDEX: PDT Plus IVD and Intravitreal Ranibizumab Versus Lucentis Monotherapy to Treat Age-Related Macular Degeneration; PDT: Photodynamic therapy; RADICAL: Reduced Fluence Visudyne-Anti-VEGF-Dexamethasone in Combination for AMD Lesions; Ran: Ranibizumab.

of Verteporfin Photodynamic Therapy and Ranibizumab Compared with Ranibizumab in Patients with Subfoveal Choroidal Neovascularization (MONT BLANC) Phase II/III trials are designed to compare ranibizumab monotherapy to ranibizumab in combination with PDT (TABLE 3).

Intravitreal corticosteroids plus anti-VEGF therapy

In a retrospective, noncomparative case series of 30 eyes of 27 patients treated with intravitreal bevacizumab and triamcinolone, the mean Snellen VA improved from 0.22 to 0.32 ($p = 0.03$) with a mean decrease in foveal thickness of $164 \mu\text{m}$ ($p < 0.001$) at first follow-up (4 weeks; range: 1–8 weeks) [39]. Other clinical trials of ocular anti-VEGF therapies in combination with corticosteroid agents are underway, such as A Prospective Study Comparing Ranibizumab Plus Dexamethasone Combination Therapy Versus Ranibizumab Monotherapy for Wet AMD (LuceDex), a Phase I/II study comparing dual therapy with ranibizumab plus dexamethasone to ranibizumab monotherapy (TABLE 3).

Triple therapy

The term ‘triple therapy’ refers to combination treatments with ocular anti-VEGF agents, intravitreal corticosteroids and PDT. In a noncomparative interventional case series of 104 patients with exudative AMD, triple therapy with bevacizumab plus verteporfin PDT and intravitreal dexamethasone improved mean VA by 1.8 lines ($p < 0.01$) and decreased mean CRT by $182 \mu\text{m}$ ($p < 0.01$) at a mean follow-up of 40 weeks [40]. The majority of patients received only a single treatment cycle. In a prospective, interventional case series of 17 patients (17 eyes) with subfoveal CNV secondary to AMD, single-session verteporfin PDT combined with triamcinolone and intravitreal bevacizumab improved mean VA from 0.74 ± 0.33 to $0.41 \pm 0.38 \log_{\text{MAR}}$ and reduced mean central macular thickness from 395 ± 181 to $221 \pm 87 \mu\text{m}$ after 24 weeks. One, two or three repeat injections of bevacizumab were given after initial triple therapy in ten, seven and two eyes, respectively [41]. In a retrospective, interventional case series of 16 patients (22 eyes) with CNV, 13 eyes had previously received treatment with triamcinolone and PDT, while nine eyes were newly diagnosed and had not previously been treated. The latter nine eyes then received treatment with intravitreal triamcinolone acetate followed by PDT and pegaptanib sodium injection at 2-week intervals. A comparison of the two groups at 6 months showed that the mean VA had improved by 2.2 lines in the newly treated triple-therapy group versus a 0.7-line mean improvement in the previously treated triamcinolone-plus-PDT group ($p = 0.013$) [42]. Ongoing randomized, prospective trials to evaluate triple therapies include the Reduced Fluence Visudyne-Anti-VEGF-Dexamethasone in Combination for AMD Lesions (RADICAL) Phase II study ($n = 160$ patients) and the PDT Plus IVD and Intravitreal Ranibizumab Versus Lucentis Monotherapy to Treat Age-Related Macular Degeneration (PDEX) Phase II study ($n = 60$ patients), both of which are evaluating ranibizumab in combination with PDT and dexamethasone (TABLE 3).

Discussion

Alternative regimens of anti-VEGF therapy for neovascular AMD, variable treatment in particular, have become the *de facto* clinical practice. Their wide adoption is based on a tacit belief in their therapeutic equivalence with standard monthly monotherapy, and some prospective and retrospective studies showing positive results with variable anti-VEGF regimens [12–15,27]. Thus far, however, the published reports of large, multicenter, randomized trials (PIER, SAILOR and HORIZON) that incorporated variable ranibizumab therapy have shown disappointing outcomes. Each of these studies had limitations in terms of infrequent patient follow-up, dosing schedules and retreatment criteria, leading many clinicians to ascribe greater significance to the PrONTO study, which demonstrated favorable 2-year outcomes using variable ranibizumab dosing on a strict variable-dosing protocol. Preliminary data from the open-label SUSTAIN trial have shown some benefits of PRN dosing following 3-monthly loading doses.

A definitive head-to-head comparison between variable and standard monthly therapy awaits the results from several ongoing clinical trials, particularly between the monthly and variable arms within the CATT study. Similarly, assessments of the equivalence or superiority of anti-VEGF combination therapies may be best made by direct comparison to monthly monotherapy, although some upcoming trials will use variable dosing as the comparison arm (TABLE 3). The expense of these novel anti-VEGF biologics has brought cost considerations to the fore in pursuing alternative regimens for neovascular AMD. In addition to the direct financial costs of the drug and procedure, other costs, including patient indisposition and practice burden, have guided the trend to alternative approaches. As ongoing clinical trials of variable and combination regimens determine the therapeutic efficacy of alternative therapies and monthly monotherapy, the ophthalmologic community may be faced with cost–benefit decisions with regard to the use of anti-VEGF therapies for patients with exudative AMD.

Expert commentary

Ocular anti-VEGF therapy has presented a major breakthrough in the care of patients with exudative AMD, giving rise to a wide array of therapeutic strategies among ophthalmologists, with no consensus on optimal practices. As an alternative to the strict regimen of monthly intravitreal injection used in the protocols of the pivotal ranibizumab clinical trials, treating physicians have adopted variable regimens reducing the frequency of injections and combination regimens using ocular anti-VEGF drugs with one or more adjuvant treatments. The goal has been to balance the patient risks, financial costs and treatment burden associated with monthly ocular anti-VEGF therapy; whether variable and combination approaches result in equivalent or superior long-term visual outcomes has, to this point, not been resolved. The conclusions that can be drawn from large randomized studies indicating less favorable therapeutic outcomes using variable ranibizumab regimens have been limited by the studies’ protocol designs and their lack of direct comparisons to monthly treatment. On the other hand, high-level evidence to support variable regimens and combination therapies has not been available;

instead, their impetus has been clinical experience, retrospective studies and a small but influential uncontrolled study of as-needed ranibizumab monotherapy.

Results from several ongoing clinical trials will provide high-level evidence to assess the relative efficacy of variable and combination therapies. In particular, the direct comparison of the variable treatment arms versus the monthly treatment arms in the upcoming CATT trial of ranibizumab and bevacizumab will have major implications for clinical practices to maximize visual outcomes for patients with exudative AMD.

Five-year view

Ocular anti-VEGF agents have significantly advanced the care of patients with exudative AMD, and are currently applied with a wide variety of therapeutic approaches. Upcoming results from key randomized clinical trials over the next several years will clarify the best practices in the management of exudative AMD with ocular anti-VEGF therapies with regard to optimal frequency of administration, duration of treatment regimen and the role of combination treatments. Cost–benefit comparisons of different approaches will also be strengthened by these upcoming

data. At the same time, novel therapies currently in development may progress to clinical availability, such as newer anti-VEGF agents, drugs with distinct pathogenetic targets, or novel modalities including intraocular radiation. These expanding treatment options will enhance patient benefits in terms of outcomes and therapeutic efficiency; maximizing these benefits will require evaluations based on high-level evidence and head-to-head clinical comparisons.

Financial & competing interests disclosure

The work was supported by Research to Prevent Blindness, the National Institutes of Health core grant (NIH-NEI EY002162), and That Man May See Foundation. Robert B Bhisitkul is on the advisory boards of Genentech, Inc. and Allergan, Inc., and is a consultant for Santen, Inc. The authors have no financial relationship with Genentech, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Support for third-party medical writing assistance for this manuscript, furnished by Robert Romanelli, was provided by Genentech, Inc.

Key issues

- In clinical practice, few retina specialists adhere to the strict schedule of regular monthly intravitreal anti-VEGF treatment injections for 2 years as established by the MARINA and ANCHOR trials of ranibizumab therapy. Rather, alternative anti-VEGF dosing regimens, including variable dosing and combination therapy, have emerged.
- Alternative anti-VEGF regimens have been employed to decrease the number and frequency of intravitreal injections to allow discontinuation of treatment upon cessation of disease activity, and to seek improved visual outcomes relative to standard therapy by combining different therapies with distinct targets of action and potentially achieving additive or synergistic effects.
- Standard monthly anti-VEGF treatment regimens are based on VEGF biology, drug pharmacokinetics and available Phase III clinical trial data.
- Large clinical trials (A Study of rhuFAB V2 [Ranibizumab] in Subjects with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration [PIER] and A Study to Evaluate Ranibizumab in Subjects With Choroidal Neovascularization [CNV] Secondary to Age-Related Macular Degeneration [SAILOR]) indicating diminishing visual benefits with variable ranibizumab regimens have not fully resolved the issue owing to protocol design discrepancies and the lack of direct comparisons to monthly injections.
- Limited data are available for combination regimens and have been primarily reported in retrospective case series or small uncontrolled studies.
- The relative therapeutic efficacy of alternative treatment regimens versus standard monthly regimens will be determined in upcoming large-scale, head-to-head clinical trials.

References

- 1 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* 116, 57–65 (2009).
- 2 Brown DM, Kaiser PK, Michels M *et al.* Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N. Engl. J. Med.* 355, 1432–1444 (2006).
- 3 Rosenfeld PJ, Brown DM, Heier JS *et al.*; for the MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N. Engl. J. Med.* 355, 1419–1431 (2006).
- 4 Bressler NM. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials – TAP report 2. *Arch. Ophthalmol.* 119, 198–207 (2001).
- 5 Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization – Verteporfin in Photodynamic Therapy report 2. *Am. J. Ophthalmol.* 131, 541–560 (2001).
- 6 Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR. Pegaptanib for neovascular age-related macular degeneration. *N. Engl. J. Med.* 351, 2805–2816 (2004).
- 7 Chakravarthy U, Adamis AP, Cunningham ET Jr *et al.* Year 2 efficacy results of 2 randomized controlled clinical trials of pegaptanib for neovascular age-related macular degeneration. *Ophthalmology* 113, 1508–1525 (2006).

- 8 Regillo CD, Brown DM, Abraham P *et al.* Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 1. *Am. J. Ophthalmol.* 145, 239–248 (2008).
- 9 D'Amico DJ, Masonson HN, Patel M *et al.*; VEGF Inhibition Study in Ocular Neovascularization (VISION) Clinical Trial Group. Pegaptanib sodium for neovascular age-related macular degeneration: two-year safety results of the two prospective, multicenter, controlled clinical trials. *Ophthalmology* 113, 992–1001 (2006).
- 10 Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. *Retina* 26, 859–870 (2006).
- 11 Wang Y, Fei D, Vanderlaan M, Song A. Biological activity of bevacizumab, a humanized anti-VEGF antibody *in vitro*. *Angiogenesis* 7, 335–345 (2004).
- 12 Aisenbrey S, Ziemssen F, Volker M *et al.* Intravitreal bevacizumab (Avastin) for occult choroidal neovascularization in age-related macular degeneration. *Graefes Arch. Clin. Exp. Ophthalmol.* 245, 941–948 (2007).
- 13 Lazic R, Gabric N. Intravitreally administered bevacizumab (Avastin) in minimally classic and occult choroidal neovascularization secondary to age-related macular degeneration. *Graefes Arch. Clin. Exp. Ophthalmol.* 245, 68–73 (2006).
- 14 Bashshur ZF, Bazarbachi A, Schakal A, Haddad ZA, El Haibi CP, Nouredin BN. Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration. *Am. J. Ophthalmol.* 142, 1–9 (2006).
- 15 Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 113, 363–372.e5 (2006).
- 16 Kim I, Ryan AM, Rohan R *et al.* Constitutive expression of VEGF, VEGFR-1, and VEGFR-2 in normal eyes. *Invest. Ophthalmol. Vis. Sci.* 40, 2115–2121 (1999).
- 17 Yi X, Ogata N, Komada M *et al.* Vascular endothelial growth factor expression in choroidal neovascularization in rats. *Graefes Arch. Clin. Exp. Ophthalmol.* 235, 313–319 (1997).
- 18 Ishibashi T, Hata Y, Yoshikawa H, Nakagawa K, Sueishi K, Inomata H. Expression of vascular endothelial growth factor in experimental choroidal neovascularization. *Graefes Arch. Clin. Exp. Ophthalmol.* 235, 159–167 (1997).
- 19 Kvant A, Algvere PV, Berglin L, Seregard S. Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor. *Invest. Ophthalmol. Vis. Sci.* 37, 1929–1934 (1996).
- 20 Gaudreault J, Fei D, Beyer JC *et al.* Pharmacokinetics and retinal distribution of ranibizumab, a humanized antibody fragment directed against VEGF-A, following intravitreal administration in rabbits. *Retina* 27, 1260–1266 (2007).
- 21 Gaudreault J, Fei D, Rusit J, Suboc P, Shiu V. Preclinical pharmacokinetics of ranibizumab (rhuFabV2) after a single intravitreal administration. *Invest. Ophthalmol. Vis. Sci.* 46, 726–733 (2005).
- 22 Beer PM, Wong SJ, Hammad AM, Falk NS, O'Malley MR, Khan S. Vitreous levels of unbound bevacizumab and unbound vascular endothelial growth factor in two patients. *Retina* 26, 871–876 (2006).
- 23 Bakri SJ, Snyder MR, Reid JM, Pulido JS, Ezzat MK, Singh RJ. Pharmacokinetics of intravitreal ranibizumab (Lucentis). *Ophthalmology* 114, 2179–2182 (2007).
- 24 Zhu Q, Ziemssen F, Henke-Fahle S *et al.*; Tübingen Bevacizumab Study Group. Vitreous levels of bevacizumab and vascular endothelial growth factor-A in patients with choroidal neovascularization. *Ophthalmology* 115, 1750–1755 (2008).
- 25 Heier JS, Antoszyk AN, Pavan PR *et al.* Ranibizumab for treatment of neovascular age-related macular degeneration: a Phase I/II multicenter, controlled, multidose study. *Ophthalmology* 113, 633–642.e4 (2006).
- 26 Rosenfeld PJ, Heier JS, Hantsbarger G, Shams N. Tolerability and efficacy of multiple escalating doses of ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Ophthalmology* 113, 623–632.e1 (2006).
- 27 Fung AE, Lalwani GA, Rosenfeld PJ *et al.* An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am. J. Ophthalmol.* 143, 566–583 (2007).
- 28 Lalwani GA, Rosenfeld PJ, Fung AE *et al.* A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTOn study. *Am. J. Ophthalmol.* 148, 43–58.e1 (2009).
- 29 Boyer DS. Safety and efficacy of ranibizumab in subjects with wet age-related macular degeneration: SAILOR cohorts 1 and 2. Presented at: *American Academy of Ophthalmology 2008 Annual Meeting*. Atlanta, GA, USA, 8–11 November 2008.
- 30 Sadda SR. HORIZON extension trial of ranibizumab [LUCENTIS] for neovascular age-related macular degeneration [AMD]: first-year safety and efficacy results. Presented at: *Retina Society Annual Meeting*. Scottsdale, AZ, USA, 25–28 September 2008.
- 31 Eldem B, Bartz-Schmidt KU, Schlingemann R *et al.*; on behalf of the EXCITE Study Group. Visual acuity response profiles in patients with neovascular age-related macular degeneration treated quarterly after 3 initial doses with ranibizumab in the EXCITE trial. Presented at: *Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO)*. Fort Lauderdale, FL, USA, 3–8 May 2009.
- 32 Holz F, Meyer C, Eter N; on behalf of the SUSTAIN study group. Safety and efficacy of ranibizumab in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration: 12-month results of the SUSTAIN trial. Presented at: *Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO)*. Fort Lauderdale, FL, USA, 3–8 May 2009.
- 33 Tatar O, Adam A, Shinoda K *et al.* Expression of VEGF and PEDF in choroidal neovascular membranes following verteporfin photodynamic therapy. *Am. J. Ophthalmol.* 142, 95–104 (2006).
- 34 Heier JS, Boyer DS, Ciulla TA *et al.* Ranibizumab in combination with verteporfin photodynamic therapy in neovascular age-related macular degeneration (FOCUS): year 1 results. *Arch. Ophthalmol.* 142, 1532–1542 (2006).
- 35 Antoszyk AN, Tuomi L, Chung CY, Singh A. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration (FOCUS): year 2 results. *Am. J. Ophthalmol.* 145, 862–874.e3 (2008).

- 36 Dhalla MS, Shah GK, Blinder KJ, Ryan EH Jr, Mittra RA, Tewari A. Combined photodynamic therapy with verteporfin and intravitreal bevacizumab for choroidal neovascularization in age-related macular degeneration. *Retina* 26, 988–993 (2006).
- 37 Ahmadieh H, Taei R, Soheilian M, Riaz-Esfahani M, Ahadi H. Single-session photodynamic therapy combined with intravitreal bevacizumab for neovascular age-related macular degeneration. *Eur. J. Ophthalmol.* 18, 297–300 (2008).
- 38 Ladewig MS, Karl SE, Hamelmann V *et al.* Combined intravitreal bevacizumab and photodynamic therapy for neovascular age-related macular degeneration. *Graefes Arch. Clin. Exp. Ophthalmol.* 246, 17–25 (2008).
- 39 Colucciello M. Intravitreal bevacizumab and triamcinolone acetate combination therapy for exudative neovascular age-related macular degeneration: short-term optical coherence tomography results. *J. Ocul. Pharmacol. Ther.* 24, 15–24 (2008).
- 40 Augustin AJ, Puls S, Offermann I. Triple therapy for choroidal neovascularization due to age-related macular degeneration: verteporfin PDT, bevacizumab, and dexamethasone. *Retina* 27, 133–140 (2007).
- 41 Ahmadieh H, Taei R, Soheilian M *et al.* Single-session photodynamic therapy combined with intravitreal bevacizumab and triamcinolone for neovascular age-related macular degeneration. *BMC Ophthalmol.* 7, 10 (2007).
- 42 Liggett PE, Colina J, Chaudhry NA, Tom D, Haffner G. Triple therapy of intravitreal triamcinolone, photodynamic therapy, and pegaptanib sodium for choroidal neovascularization. *Am. J. Ophthalmol.* 142, 1072–1074 (2006).
- Websites**
- 101 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 <http://clinicaltrials.gov/ct2/show/NCT00379795>
- 102 A Study to Evaluate Ranibizumab in Subjects with Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD) <http://clinicaltrials.gov/ct2/show/NCT00251459>
- 103 EXCITE – Efficacy and Safety of Ranibizumab in Patients With Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (ARMD) <http://clinicaltrials.gov/ct2/show/NCT00275821>
- 104 SUSTAIN – Study of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration <http://clinicaltrials.gov/ct2/show/NCT00331864>
- 105 Comparison of Age-related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial <http://clinicaltrials.gov/ct2/show/NCT00593450>
- 106 IVAN trial summary page www.ivan-trial.co.uk
- 107 Manta Study: Avastin Versus Lucentis in Age Related Macular Degeneration (MANTA) <http://clinicaltrials.gov/ct2/show/NCT00710229>
- 108 Prevention of Vision Loss in Patients with Age-Related Macular Degeneration (AMD) by Intravitreal Injection of Bevacizumab and Ranibizumab (VIBERA) <http://clinicaltrials.gov/ct2/show/NCT00559715>
- 109 Combined PDT and Intravitreal Bevacizumab vs Combination of PDT, Intravitreal Bevacizumab and Triamcinolone for Neovascular AMD <http://clinicaltrials.gov/ct2/show/NCT00370539>
- 110 Efficacy/Safety of Verteporfin Photodynamic Therapy and Ranibizumab Compared with Ranibizumab in Patients With Subfoveal Choroidal Neovascularization <http://clinicaltrials.gov/ct2/show/NCT00436553>
- 111 Verteporfin Photodynamic Therapy Administered in Conjunction With Ranibizumab in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration (AMD) <http://clinicaltrials.gov/ct2/show/NCT00433017>
- 112 Safety and Efficacy Study Evaluating the Combination of Bevasiranib & Lucentis Therapy in Wet AMD (CARBON) <http://clinicaltrials.gov/ct2/show/NCT00557791>
- 113 A Study of Strontium⁹⁰ β Radiation With Lucentis to Treat Age-Related Macular Degeneration (CABERNET) <http://clinicaltrials.gov/ct2/show/NCT00454389>
- 114 A Prospective Study Comparing Ranibizumab Plus Dexamethasone Combination Therapy Versus Ranibizumab Monotherapy for Wet AMD (Lucedex) <http://clinicaltrials.gov/ct2/show/NCT00793923>
- 115 Reduced Fluence Visudyne-Anti-VEGF-Dexamethasone In Combination for AMD Lesions (RADICAL) <http://clinicaltrials.gov/ct2/show/NCT00492284>
- 116 Triple Therapy – PDT Plus IVD and Intravitreal Ranibizumab Versus Lucentis Monotherapy to Treat Age-Related Macular Degeneration (PDEX) <http://clinicaltrials.gov/ct2/show/NCT00390208>