Eye (2008) 22, 761–767

www.nature.com/eye

REVIEW

The evolving role of vascular endothelial growth factor inhibitors in the treatment of neovascular age-related macular degeneration

H Dadgostar and N Waheed

Abstract

Age-related macular degeneration (AMD) is the leading cause of blindness among the ageing population. The introduction of molecular inhibitors of vascular endothelial growth factor (VEGF), such as pegaptanib, ranibizumab, and bevacizumab, as treatments for exudative AMD has provided new hope for affected patients and has transformed the practices of retina specialists. Phase III clinical trials have demonstrated the efficacy and safety of monthly ranibizumab for the preservation as well as improvement of visual acuity in patients with exudative AMD. Ongoing trials are evaluating the effectiveness of different dosing regimens, monitoring strategies, and combination therapies to determine the optimal niche for this new class of drugs in AMD management. Based on emerging evidence, most clinicians are now adopting a variable VEGF inhibitor dosing strategy guided by serial diagnostic re-evaluation by optical coherence tomography. Some are also finding benefit through the addition of photodynamic therapy and steroids to the treatment regimen. The results of current and upcoming trials systematically addressing these issues are expected to establish new guidelines for the management of AMD. Indeed, a new paradigm may emerge wherein numerous modular therapeutic modalities are administered in customized combinations based on specific clinical and diagnostic findings.
Eye (2008) **22,** 761–767; doi:10.1038/eye.2008.86; published online 4 April 2008

Keywords: VEGF; age related macular degeneration; Intravitreal injection

Introduction

The introduction of inhibitors of vascular endothelial growth factor (VEGF)-A to the world of ophthalmology has transformed the management of age-related macular degeneration (AMD), the leading cause of blindness among the ageing population in the developing world.[1] Retina specialists have largely embraced this new class of medication, which has for the first time offered the hope of visual improvement to patients suffering from AMD. Although a large body of data supports the efficacy of intravitreal injections of VEGF inhibitors in AMD, the incorporation of this new treatment modality into a management plan remains a challenge for many practitioners because of the current lack of standardized evidence-based guidelines for treatment and follow-up. In the present review, we highlight the findings of the major clinical studies on VEGF inhibitors for the treatment of AMD, discuss emerging management patterns, and briefly examine future directions in the field.

Abnormal angiogenesis is believed to play an important role in the development and progression of exudative AMD as well as proliferative retinopathies and systemic diseases such as cancer.[2] On the cellular level, a simplified model of angiogenesis involves a balance between proangiogenic molecules, such as transforming growth factor (TGF)-α and TGF-β, the angiopoietins, and members of the VEGF

Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

Correspondence: N Waheed, Department of Ophthalmology, The Cole Eye Institute, Cleveland Clinic Foundation, Jan-32, 9500 Euclid Avenue, Cleveland, OH 44195, USA
Tel: +1 216 445 9432; Fax: +1 216 445 2226.
E-mail: waheedn@ccf.org

Received: 16 October 2007
Accepted in revised form: 19 February 2008
Published online: 4 April 2008

family, and antiangiogenic factors, such as pigment epithelium-derived factor, thrombospondin, and angiostatin.[2,3] VEGF-A is a member of a pleiotropic multigene family, and multiple splice variants of this molecule have been described with roles in angiogenesis as well as vascular permeability and possibly cell survival.[4–6] The biologically active secreted form is a homodimer that binds the receptor tyrosine kinases VEGF receptor (VEGFR)-1 and VEGFR-2 on endothelial cells to induce intracellular tyrosine kinase pathways.[3,4] In AMD, VEGF-A is believed to be important for the growth and maintenance of choroidal neovascularization (CNV) and has been detected in high levels both within excised CNV specimens and in the vitreous of patients with subretinal CNV.[7,8] This hypothesis ultimately led to the development of pegaptanib sodium and ranibizumab, the first United States Food and Drug Administration (FDA)-approved biologically targeted treatments for exudative AMD.

Pegaptanib and ranibizumab: clinical efficacy trials

Pegaptanib sodium (Macugen™; OSI-Eyetech, New York, NY, USA), the first FDA-approved anti-VEGF therapy for AMD, is a pegylated oligonucleotide aptamer with high binding specificity for the $VEGF_{165}$ splice isoform.[9] The VEGF Inhibition Study in Ocular Neovascularization (VISION) study consisted of two prospective, randomized, double-masked, sham-controlled phase III clinical trials demonstrating the efficacy of intravitreal pegaptanib (*vs* sham injection) for the treatment of exudative AMD (Table 1).[10–12] Subjects with exudative AMD were enrolled without regard to angiographic lesion subtype and were randomized to one of three doses of pegaptanib or sham injection every 6 weeks for 48 weeks, with the exception of subjects with predominantly classic lesions who also underwent photodynamic therapy (PDT) at the discretion of a masked treating ophthalmologist. At 12 months, 70% of subjects receiving 0.3 mg pegaptanib lost fewer than 15 letters of visual acuity compared to 55% of subjects in the sham group ($P<0.001$). Serious adverse ocular events related to the injection procedure included endophthalmitis (1.3%) and retinal detachment (0.6%).

Ranibizumab (Lucentis™; Genentech, South San Francisco, CA, USA) was developed using the same murine monoclonal antigen-binding site as bevacizumab (Avastin™; Genentech), a humanized anti-VEGF monoclonal antibody that received FDA approval in 2004 for the treatment of metastatic colorectal cancer.[3,13] Unlike the full-length bevacizumab, which retains both of its antigen-binding sites, ranibizumab has a single antigen-binding site because it was derived by affinity

Table 1 One-year data from the major randomized, controlled clinical trials of VEGF inhibitors for exudative AMD

Study	*Treatment*	*% Losing <15 letters (P vs control)*	*% Gaining ⩾15 letters (P vs control)*	*Control*	*% Losing <15 letters*	*% Gaining ⩾15 letters*	*Interval*	*Angiographic lesion type*
Vision	Peg 0.3 mg ($n=297$)	70 ($P<0.001$)	6 ($P=0.04$)	Sham ($n=304$)	55	2	6 weeks fixed	All
	Peg 1.0 mg ($n=305$)	71 ($P<0.001$)	7 ($P=0.02$)					
	Peg 3.0 mg ($n=302$)	65 ($P=0.03$)	4 ($P=0.16$)					
Marina	Ran 0.3 mg ($n=238$)	94.5 ($P<0.001$)	24.8 ($P<0.001$)	Sham ($n=238$)	62.2	5	1 month fixed	Minimally classic; occult with no classic
	Ran 0.5 mg ($n=240$)	94.6 ($P<0.001$)	33.8 ($P<0.001$)					
Anchor	Ran 0.3 mg ($n=140$)	94.3 ($P<0.001$)	35.7 ($P<0.001$)	PDT ($n=143$)	64.3	5.6	1 month fixed (Ran); 3 month PRN (PDT)	Predominantly classic
	Ran 0.5 mg ($n=139$)	96.4 ($P<0.001$)	40.3 ($P<0.001$)					
Focus	Ran 0.5 mg + PDT ($n=105$)	90 ($P=0.0003$)	24 ($P=0.003$)	Sham + PDT ($n=56$)	68	5	1 month fixed (Ran); 3 month PRN (PDT)	Predominantly classic

maturation of a humanized Fab fragment of the original monoclonal anti-VEGF antibody. Ranibizumab, like bevacizumab, binds all active isoforms of VEGF-A and is thus considered a non-selective VEGF-A inhibitor.[14,15]

The safety and efficacy of ranibizumab were evaluated in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) trial, a 2-year, prospective, randomized, double-masked, sham-controlled trial (Table 1).[16] Subjects enrolled in the study were randomized to receive one of two doses of intravitreal ranibizumab or sham injections every month for a total of 24 injections over 2 years. At 12 months, 95% of subjects receiving ranibizumab lost fewer than 15 letters of visual acuity compared to 62% of subjects receiving sham injections ($P<0.001$). In addition, 25% of subjects treated with 0.3 mg ranibizumab and 34% of subjects treated with 0.5 mg ranibizumab gained 15 letters or more of visual acuity compared to 5% of subjects in the control arm ($P<0.001$). These improvements were maintained at 24 months of follow-up. Serious ocular adverse events included endophthalmitis (1.0%) and uveitis (1.3%).

Similar findings were reported in the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) trial, another 2-year, prospective, randomized, double-masked, sham-controlled trial comparing ranibizumab with PDT.[17] Subjects were randomized to one of two doses of intravitreal ranibizumab every month for 2 years or PDT on study entry and every 3 months as needed according to accepted guidelines for 2 years. At 12 months, 94–96% of subjects treated with ranibizumab lost fewer than 15 letters of visual acuity compared with 64% of those in the PDT group ($P<0.001$). Also, 36% of subjects receiving 0.3 mg ranibizumab and 40% of those receiving 0.5 mg ranibizumab gained 15 letters or more of visual acuity compared to 6% of those receiving PDT (Table 1). Serious ocular adverse events in the ranibizumab group included endophthalmitis and uveitis (<1%), as in the MARINA study.

The RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety (FOCUS) trial, a prospective, randomized, single-masked phase I–II study, evaluated ranibizumab in combination with PDT compared to PDT alone (Table 1).[18] Subjects with predominantly classic lesions received PDT on study entry followed by monthly ranibizumab (0.5 mg) or sham injections for 2 years. PDT was repeated as needed at 3-month intervals according to angiographic guidelines. The findings resembled those of the above studies with 90% of subjects in the combination group losing less than 15 letters of visual acuity compared to 68% of subjects in the PDT group ($P=0.0003$) and 24% of subjects in the combination group gaining 15 letters or more compared to 5% in the PDT group. Together, these studies helped establish intravitreal ranibizumab not only as a safe and efficacious treatment for exudative AMD but also as a treatment capable of producing visual gain in a significant proportion of patients.

Bevacizumab

A major challenge in the management of patients who require repeated anti-VEGF injections is the cost of ranibizumab.[19,20] Bevacizumab, as mentioned above, is a full-length humanized anti-VEGF monoclonal antibody with essentially the same specificity as ranibizumab;[3] however, the cost of an intravitreal dose of bevacizumab, which is marketed in much larger quantities for intravenous administration in cancer patients, is much lower.

In a prospective case series, Chen *et al*[21] report that in 102 eyes receiving monthly 1.25 mg bevacizumab injections until resolution of leakage, mean visual acuity at 14 weeks of follow-up improved from 20/80 to 20/50 and macular thickness by optical coherence tomography (OCT) improved from 251 to 210 μm ($P<0.05$). Similarly, Spaide *et al*[22] report that in a retrospective study of 266 consecutive eyes receiving bevacizumab for neovascular AMD, at 3 months of follow-up, the mean visual acuity improved from 20/184 to 20/109 ($P<0.001$), with 38.3% of eyes demonstrating improvement in visual acuity. A number of other small short-term studies have reported similar promising results, both in terms of decreased retinal thickness on OCT and visual acuity preservation.[23–27]

Despite these promising data, no large clinical trial has yet addressed the efficacy of this drug in AMD. Treatment guidelines for the use of bevacizumab are also more poorly defined than for ranibizumab, and clinicians often apply the same dosing and follow-up criteria for both drugs, although the effective intraocular half-lives of the two drugs may not be the same.[28] Obtaining sponsorship for a head-to-head comparison of bevacizumab and ranibizumab has been challenging, as both drugs (Avastin and Lucentis) are made by Genentech; however, the Comparison of Age-Related Macular Degeneration Treatments Trial (CATT), supported by the United States National Eye Institute, is expected to begin recruiting subjects soon. This large clinical trial will directly compare ranibizumab and bevacizumab for the treatment of exudative AMD and is anticipated to answer many of the questions regarding the efficacy of this drug as well as directly comparing fixed dosing to as needed dosing.

Safety

As mentioned above, the incidence of serious ocular adverse events, including endophthalmitis, severe uveitis, and rhegmatogenous retinal detachment, was similar for subjects receiving ranibizumab in both the MARINA and ANCHOR trials, not exceeding 1.3% for any given adverse outcome.[16,17] Endophthalmitis and retinal detachment are injection-related events, and more recent data based on a larger number of injections suggest that the actual rates of injection-related complications may in fact be significantly lower than those found in these initial trials. The Pan-American Collaborative Retina Study Group (PACORES) recently reported 12-month safety data on 1.25 and 2.5 mg doses of intravitreal bevacizumab.[29] Based on 4303 injections in 1310 eyes, the reported risks of serious ocular adverse events, such as endophthalmitis (0.16%) and rhegmatogenous retinal detachment (0.02%), were low. Systemic adverse events such as cerebrovascular accidents (0.5%) and myocardial infarctions (0.4%) were also uncommon. The International Intravitreal Bevacizumab Safety Survey is an internet-based survey of safety data from 70 centres in 12 countries reporting on more than 7000 injections. Event rates for a variety of ocular and systemic adverse events have been analysed, including corneal abrasion, lens injury, retinal detachment, uveitis, endophthalmitis, central retinal artery occlusion, subretinal haemorrhage, retinal pigment epithelium tears, transient ischaemic attack, cerebrovascular accident, and death, and no individual event rate exceeded 0.21%.[30]

Concerns about systemic drug-related adverse events arose as a result of data on arterial thromboembolism associated with systemic administration of this class of drugs,[31] although the expected systemic impact of an intravitreal dose is a small fraction of that of an intravenous dose. Similar rates of systemic arterial thromboembolic events were reported in the MARINA and ANCHOR trials. In the MARINA trial, there was no significant difference between subgroups in the rate of ischaemic stroke (0.8% in sham group, 1.3% in 0.3 mg group, 2.5% in 0.5 mg group) or myocardial infarction (1.7% in sham group, 2.5% in 0.3 mg group, 1.3% in 0.5 mg group). Likewise, in the ANCHOR trial, one subject in each group (0.7%) suffered a cerebrovascular accident and the rates of myocardial infarction did not significantly differ (0.7% in PDT group, 0.7% in 0.3 mg group, 2.1% in 0.5 mg group).

Despite the lack of statistical significance, some suggestive trends in the rates of systemic adverse events warrant further investigation in trials enrolling larger populations. The Safety Assessment of Intravitreal Lucentis for AMD (SAILOR) trial is an ongoing study enrolling roughly 5000 subjects. A recent interim analysis from this trial revealed 1.2% incidence of stroke in the 0.5 mg ranibizumab group compared to 0.3% in the 0.3 mg group ($P = 0.02$), suggesting that a dose-dependent increase in the rate of thromboembolic events may indeed exist and prompting the manufacturer of the drug to issue a warning letter to physicians in January 2007.[32] By comparison, in a retrospective analysis of the United States Medicare database from 2001 to 2003, the in-patient ischaemic stroke rates for 15 771 patients with exudative AMD and 46 408 matched controls were 3.5 and 3.6%, respectively, increasing to 35.1% among those with a history of previous arterial thromboembolic events.[33] Thus, while more data are needed to settle this issue, most practitioners still feel that stroke rates among patients receiving intravitreal anti-VEGF agents are likely comparable to background stroke rates in this population and that even a small potential risk may not outweigh the benefits of treatment as long as it is discussed with patients prior to initiation of therapy.

Spacing and duration of anti-VEGF injections and follow-up

Although anti-VEGF therapy is accepted by most as the current standard of care for exudative AMD, there is considerable variation in management strategies with regard to follow-up as well as frequency and duration of treatments. In the ANCHOR and MARINA studies, subjects received monthly injections of ranibizumab for 2 years with no designated clinical end point for treatment cessation.[16,17] The Phase IIIb, Multi-center, Randomized, Double-masked, Sham Injection-controlled Study of the Efficacy and Safety of Ranibizumab (PIER) attempted to address the issue of treatment frequency by evaluating a regimen of three 1-monthly injections on enrolment, followed by an injection every 3 months for a total of 2 years. At 12 months, subjects treated with ranibizumab had essentially unchanged vision, whereas sham-treated subjects lost approximately 16 letters of visual acuity ($P < 0.0001$).[34] Although ranibizumab remains beneficial, the results appear less impressive than those of the ANCHOR and MARINA studies, suggesting that simply increasing the time between injections may compromise treatment results. It is important to note, however, that the control group in the PIER study also did more poorly than the controls in the other studies, suggesting that some of the difference between these studies may reflect differences among the subject populations.

In the Prospective OCT Imaging of Patients with Neovascular AMD Treated with Intra-ocular Lucentis (PrONTO) study, a single-site, open-label, FDA-reviewed, investigator-sponsored trial, subjects

received three 1-monthly injections (months 0, 1, and 2) and thereafter received treatment based on serial OCT findings. Thus, variable dosing was custom-tailored for each subject based on OCT analyses, which often detected small amounts of fluid prior to clinically apparent anatomic changes. Data at 12 months show that 95% of subjects lose fewer than 15 letters of visual acuity and 35% of subjects gain 15 letters or more of visual acuity.[35] Significant benefit is maintained at 2 years, with 43% gaining 15 letters or more of visual acuity with a mean of five injections per year.[36]

PrONTO is a smaller study; however, it demonstrates the utility of OCT as a tool for serial reassessment on follow-up and suggests that in conjunction with this tool, reduced dosing of ranibizumab may successfully sustain visual gain after three monthly doses. The much larger SAILOR trial is currently ongoing and is expected to provide more information on the efficacy of variable dosing regimens.[37] For the present, many clinicians are following variations of the PrONTO regimen of three monthly injections followed by retreatment as needed based on serial OCT evaluations.

The frequency of follow-up visits is another area where clear guidelines are lacking. Currently, there are no significant data supporting an optimal follow-up frequency. Thus, some clinicians are following the monthly intervals established by the ANCHOR and MARINA studies. Others are using the presence or absence of fluid on serial OCT scans to guide the spacing of future follow-up visits at variable intervals based largely on personal experience.

Combination therapies

VEGF inhibitors have largely replaced PDT as the first-line therapy for subfoveal CNV; however, many are re-examining PDT as an adjunctive modality to decrease the frequency of injections and possibly augment treatment effect. The FOCUS study compared combination ranibizumab/PDT treatment with PDT alone and found a significant benefit in the combination group;[18] however, it is important to note that there was no ranibizumab monotherapy group in this study. Comparisons across studies suggest similar levels of vision preservation and improvement between the combination group in the FOCUS study and the ranibizumab group in the ANCHOR study. Clinical trials directly comparing the safety and efficacy of combination PDT/ranibizumab therapy with ranibizumab monotherapy (the DENALI and MONT BLANC studies) are currently recruiting subjects and are expected to provide much needed data on this issue. Some have also found success with combination therapy using anti-VEGF, PDT and intravitreal dexamethasone (ie, 'triple therapy') as an alternative combination regimen.[38]

Noteworthy in the discussion of combination therapies is the concept of reduced-fluence PDT. Data from the Verteporfin in Minimally Classic CNV (VIM) study suggest that a reduced dose of light energy delivered via PDT is at least as effective as or more effective than standard PDT in preserving vision in subjects with minimally classic lesions.[39] The exact nature of the destructive effect of PDT and the role of decreased energy in modulating this effect are not clear; however, concerns about the long-term destructive effects of standard PDT have made reduced-fluence combination therapies an attractive possibility. Although there are currently no data on how best to achieve the optimal energy for PDT treatment, clinicians have tried varying multiple parameters, including actual energy per unit area, number of seconds of light exposure, and dose of intravenous verteporfin. Data from upcoming combination therapy trials are anticipated to further clarify the role of low-fluence PDT in treating exudative AMD and reducing anti-VEGF injection frequencies.

Future combination therapies may also employ new pharmaceutical agents in conjunction with current VEGF inhibitors. The Bridging Industry and the National Eye Institute (BRIDGE) study intends to investigate the combination of 6-month juxtascleral anecortave acetate injections with intravitreal ranibizumab dosing on an as-needed basis with OCT guidance. Anecortave acetate is a synthetic cortisol analogue that has been shown to preserve vision in exudative AMD with tissue retention of active drug levels for up to 6 months.[40,41]

Summary

VEGF inhibitors have rapidly become the first-line therapy for exudative AMD and have significantly altered the practice of many retina specialists. Ranibizumab, administered in monthly intravitreal doses, may be the most effective treatment presently available for exudative AMD, although the relative efficacy of different members of this drug class will become clearer after direct comparisons, such as the upcoming CATT trial. Although the risks of intravitreal injections are small, serious ocular adverse events have been reported, making it desirable to reduce the frequency of injections as much as possible without compromising treatment benefit. Questions about optimal dosing frequency, follow-up interval, outcome measures, and the role of current VEGF inhibitors in the context of existing and emerging treatment modalities are crucial to the development of consistent management guidelines. Answers to such questions are only beginning to emerge from ongoing clinical trials;

however, it appears at this time that it may be possible to reduce the frequency of injections without compromising therapeutic benefit when careful follow-up and serial OCT scans are used to guide treatment. It is possible that the combination of low-fluence PDT with VEGF inhibitors may augment treatment effect and reduce injection frequency, but any firm conclusions on this issue will have to await the outcomes of ongoing clinical trials. Ultimately, a better understanding of the prognostic significance of baseline lesion characteristics and early treatment responses may be necessary to select one of multiple optimal treatment regimens for a given case.

References

1 Bressler NM. Age-related macular degeneration is the leading cause of blindness. *JAMA* 2004; **291**: 1900–1901.
2 Ferrara N. Role of vascular endothelial growth factor in physiologic and pathologic angiogenesis: therapeutic implications. *Semin Oncol* 2002; **29**: 10–14.
3 Kaiser PK. Antivascular endothelial growth factor agents and their development: therapeutic implications in ocular diseases. *Am J Ophthalmol* 2006; **142**: 660–668.
4 Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev* 2004; **25**: 581–611.
5 Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science* 1989; **246**: 1306–1309.
6 Nagy JA, Vasile E, Feng D, Sundberg C, Brown LF, Detmar MJ *et al*. Vascular permeability factor/vascular endothelial growth factor induces lymphangiogenesis as well as angiogenesis. *J Exp Med* 2002; **196**: 1497–1506.
7 Kvanta A, Algvere PV, Berglin L, Seregard S. Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor. *Invest Ophthalmol Vis Sci* 1996; **37**: 1929–1934.
8 Wells JA, Murthy R, Chibber R, Nunn A, Molinatti PA, Kohner EM *et al*. Levels of vascular endothelial growth factor are elevated in the vitreous of patients with subretinal neovascularisation. *Br J Ophthalmol* 1996; **80**: 363–366.
9 Ruckman J, Green LS, Beeson J, Waugh S, Gillette WL, Henninger DD *et al*. 2′-Fluoropyrimidine RNA-based aptamers to the 165-amino acid form of vascular endothelial growth factor (VEGF165). Inhibition of receptor binding and VEGF-induced vascular permeability through interactions requiring the exon 7-encoded domain. *J Biol Chem* 1998; **273**: 20556–20567.
10 Chakravarthy U, Adamis AP, Cunningham Jr ET, Goldbaum M, Guyer DR, Katz B *et al*. Year 2 efficacy results of 2 randomized controlled clinical trials of pegaptanib for neovascular age-related macular degeneration. *Ophthalmology* 2006; **113**: 1508 e1–25.
11 D'Amico DJ, Masonson HN, Patel M, Adamis AP, Cunningham Jr ET, Guyer DR *et al*. Pegaptanib sodium for neovascular age-related macular degeneration: two-year safety results of the two prospective, multicenter, controlled clinical trials. *Ophthalmology* 2006; **113**: 992–1001 e6.
12 Gragoudas ES, Adamis AP, Cunningham Jr ET, Feinsod M, Guyer DR. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004; **351**: 2805–2816.
13 Kim KJ, Li B, Houck K, Winer J, Ferrara N. The vascular endothelial growth factor proteins: identification of biologically relevant regions by neutralizing monoclonal antibodies. *Growth Factors* 1992; **7**: 53–64.
14 Chen Y, Wiesmann C, Fuh G, Li B, Christinger HW, McKay P *et al*. Selection and analysis of an optimized anti-VEGF antibody: crystal structure of an affinity-matured Fab in complex with antigen. *J Mol Biol* 1999; **293**: 865–881.
15 Rosenfeld PJ, Schwartz SD, Blumenkranz MS, Miller JW, Haller JA, Reimann JD *et al*. Maximum tolerated dose of a humanized anti-vascular endothelial growth factor antibody fragment for treating neovascular age-related macular degeneration. *Ophthalmology* 2005; **112**: 1048–1053.
16 Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY *et al*. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355**: 1419–1431.
17 Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY *et al*. Ranibizumab *vs* verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355**: 1432–1444.
18 Preliminary phase I/II data show Lucentis in combination with Visudyne maintained or improved vision in approximately 90 percent of patients with wet age-related macular degeneration. http://www.gene.com/gene/news/press-releases/display.do?method = detail&id = 8467&categoryid = 3 2005.
19 Freeman WR, Falkenstein I. Avastin and new treatments for AMD: where are we? *Retina* 2006; **26**: 853–858.
20 Raftery J, Clegg A, Jones J, Tan SC, Lotery A. Ranibizumab (Lucentis) *vs* bevacizumab (Avastin): modelling cost effectiveness. *Br J Ophthalmol* 2007; **91**: 1244–1246.
21 Chen CY, Wong TY, Heriot WJ. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration: a short-term study. *Am J Ophthalmol* 2007; **143**: 510–512.
22 Spaide RF, Laud K, Fine HF, Klancnik Jr JM, Meyerle CB, Yannuzzi LA *et al*. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006; **26**: 383–390.
23 Aisenbrey S, Ziemssen F, Volker M, Gelisken F, Szurman P, Jaissle G *et al*. Intravitreal bevacizumab (Avastin) for occult choroidal neovascularization in age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2007; **245**: 941–948.
24 Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 2006; **113**: 363–372 e5.
25 Chen E, Kaiser RS, Vander JF. Intravitreal bevacizumab for refractory pigment epithelial detachment with occult choroidal neovascularization in age-related macular degeneration. *Retina* 2007; **27**: 445–450.
26 Rich RM, Rosenfeld PJ, Puliafito CA, Dubovy SR, Davis JL, Flynn Jr HW *et al*. Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Retina* 2006; **26**: 495–511.
27 Emerson MV, Lauer AK, Flaxel CJ, Wilson DJ, Francis PJ, Stout JT *et al*. Intravitreal bevacizumab (Avastin) treatment of neovascular age-related macular degeneration. *Retina* 2007; **27**: 439–444.
28 Gaudreault J, Fei D, Rusit J, Suboc P, Shiu V. Preclinical pharmacokinetics of Ranibizumab (rhuFabV2) after a single intravitreal administration. *Invest Ophthalmol Vis Sci* 2005; **46**: 726–733.

29 Wu L, Martinez-Castellanos MA, Quiroz-Mercado H, Arevalo JF, Berrocal MH, Farah ME *et al*. Twelve-month safety of intravitreal injections of bevacizumab (Avastin(R)): results of the Pan-American collaborative retina study group (PACORES). *Graefes Arch Clin Exp Ophthalmol* 2007; **246**: 81–87.
30 Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. *Br J Ophthalmol* 2006; **90**: 1344–1349.
31 Scappaticci FA, Skillings JR, Holden SN, Gerber HP, Miller K, Kabbinavar F *et al*. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst* 2007; **99**: 1232–1239.
32 Dafer RM, Schneck M, Friberg TR, Jay WM. Intravitreal ranibizumab and bevacizumab: a review of risk. *Semin Ophthalmol* 2007; **22**: 201–204.
33 Alexander SL, Linde-Zwirble WT, Werther W, Depperschmidt EE, Wilson LJ, Palanki R *et al*. Annual rates of arterial thromboembolic events in Medicare neovascular age-related macular degeneration patients. *Ophthalmology* 2007; **114**: 2174–2178.
34 Preliminary results from a phase IIIb study showed patients with wet AMD treated with Lucentis quarterly experienced a 16-letter benefit over the control group at one year. http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=9747&categoryid=4 2006.
35 Rosenfeld PJ, Fung AE, Lawani GA, Michels S, Venkatraman AS, Puliafito CA. Visual acuity outcomes following a variable-dosing regimen for ranibizumab (Lucentis) in neovascular AMD: The PrONTO study. *Presented at Annual Meeting of the Association for Research in Vision and Ophthalmology*; Fort Lauderdale, FL; 2 May 2006.
36 Puliafito CA. An OCT-guided variable dosing regimen with ranibizumab (Lucentis) in neovascular AMD: two year results of the PrONTO study. *Presented at Annual Advanced Vitreoretinal Techniques and Technology Conference*; Chicago, IL; 8 September 2007.
37 Rosenfeld PJ, Rich RM, Lalwani GA. Ranibizumab: phase III clinical trial results. *Ophthalmol Clin North Am* 2006; **19**: 361–372.
38 Augustin AJ, Puls S, Offermann I. Triple therapy for choroidal neovascularization due to age-related macular degeneration: verteporfin PDT, bevacizumab, and dexamethasone. *Retina* 2007; **27**: 133–140.
39 Azab M, Boyer DS, Bressler NM, Bressler SB, Cihelkova I, Hao Y *et al*. Verteporfin therapy of subfoveal minimally classic choroidal neovascularization in age-related macular degeneration: 2-year results of a randomized clinical trial. *Arch Ophthalmol* 2005; **123**: 448–457.
40 Clarke MS. Anecortave acetate. *Ophthalmology* 2004; **111**: 2316; author reply 2316–2317.
41 D'Amico DJ, Goldberg MF, Hudson H, Jerdan JA, Krueger DS, Luna SP *et al*. Anecortave acetate as monotherapy for treatment of subfoveal neovascularization in age-related macular degeneration: twelve-month clinical outcomes. *Ophthalmology* 2003; **110**: 2372–2383; discussion 2384–2385.