Current Strategies for the Management of Treatment-Resistant Neovascular Age-Related Macular Degeneration

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Published online: 13 December 2013
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Abstract While intravitreal anti-vascular endothelial growth factor (VEGF) therapy is currently the standard of care for the treatment of neovascular age-related macular degeneration, there are some eyes which show varying degrees of treatment resistance manifested as persistent or increasing signs of exudation, often associated with vision loss. Numerous therapeutic strategies have been proposed to manage these challenging cases including increasing the dose of the same anti-VEGF agent, increasing the frequency of administration of anti-VEGF therapy, switching to a different anti-VEGF agent, and combining anti-VEGF therapy with another treatment modality, most commonly verteporfin photodynamic therapy. This manuscript will review our definition of treatment resistance, discuss its possible causes, and review the rationale and outcomes for the various management options used in these patients.

Keywords Neovascular age-related macular degeneration · Choroidal neovascularization · Tachyphylaxis · Treatment resistance · Triamcinolone · Intravitreal anti-vascular endothelial growth factor (VEGF)

Introduction

Historical Perspective

Intravitreal anti-vascular endothelial growth factor (VEGF) therapy was established as the standard of care for the treatment of neovascular age-related macular degeneration (AMD) in two landmark clinical trials ANCHOR (Predominantly Classic Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) [1] and MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) [2] that evaluated monthly intravitreal injections of humanized monoclonal antibody fragment ranibizumab (Lucentis®, Genentech, Inc., South San Francisco, CA; and Novartis, Basel, Switzerland) in eyes with new-onset neovascular AMD. For the first time, vision could be stabilized in 90 % of treated eyes (defined as a loss of fewer than 15 letters) and even improved in 34–41 % of eyes after 24 months of follow-up [1–3].

Prior to the commercial availability of ranibizumab, retina specialists began using off-label bevacizumab (Avastin®, Genentech, Inc., South San Francisco, CA; and F. Hoffmann-La Roche, Basel, Switzerland), a recombinant full-length antibody derived from the same murine humanized monoclonal antibody precursor as ranibizumab, to treat neovascular AMD with outcomes that seemed similar to those seen in the ANCHOR and MARINA trials.

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This positive experience led to the randomized 2-year clinical trial CATT (Comparison of AMD Treatment Trials), sponsored by the National Institutes of Health, which enrolled 1,185 patients. CATT showed that monthly bevacizumab was not inferior to ranibizumab for the treatment of neovascular AMD [4, 5•]. A similar clinical trial called IVAN (The Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularization) was conducted in England and Northern Ireland (610 patients) and showed similar results [6, 7•].

A third anti-VEGF agent, aflibercept (VEGF Trap-Eye, Eylea; Regeneron, Tarrytown, New York, USA, and Bayer, Berlin, Germany), recently became commercially available to treat neovascular AMD. Aflibercept is a soluble decoy receptor produced by fusing all-human DNA sequences of the second immunoglobulin domain of human VEGFR1 and the third immunoglobulin domain of human VEGFR2, which then EW fused to the Fc region of human IgG1.2. The pivotal clinical trials of aflibercept, VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) 1 and VIEW 2 showed that, at 1 year, aflibercept treatment (0.5, 2 mg monthly, or 2 mg every 2 months after three initial monthly doses) was non-inferior and clinically equivalent to ranibizumab (0.5 mg) given monthly [8•].

Long-Term Results with Intravitreal Anti-VEGF Therapy

There is little in the literature describing the long-term visual outcomes in eyes receiving intravitreal anti-VEGF therapy for neovascular AMD. Rofagha et al. looked at a cohort of 65 patients approximately 7 years after their enrollment in the ANCHOR and MARINA trials. These eyes were evaluated in a cross-sectional cohort study called SEVEN-UP [9•]. Approximately one-third demonstrated visual acuity of 20/70 or better, one quarter 20/40 or better and almost half of eyes were stable whereas one-third declined by 15 letters or more. Macular RPE atrophy was detected by FAF imaging in 98 % of eyes, and the area of RPE atrophy was significantly correlated with poor visual outcome [9•]. While patients in SEVEN-UP were treated at the discretion of their physicians, these results emphasize that neovascular AMD is a chronic disease and that these patients are at risk for vision loss many years after treatment initiation, even if the treatment response was initially optimal [9•].

Current Definition of Treatment Resistant Neovascular AMD

The CATT trial showed that even with monthly retreatment with either ranibizumab or bevacizumab, more than 50 % of eyes will manifest persistent fluid on OCT [4, 5•].

Despite persistent fluid in the majority of cases, eyes in CATT still achieved a mean visual improvement that was maintained for the 2-year duration of the study. Similarly, we have observed that some eyes with persistent fluid despite monthly anti-VEGF therapy, particularly those with subretinal fluid overlying type 1 (sub-RPE) neovascular lesions, may maintain stable visual acuity for five or more years of treatment. Therefore, we feel it is appropriate to consider both the presence of macular exudation (fluid and/or hemorrhage) and visual function when defining treatment resistance. Eyes can be sub-divided into “incomplete responders” in which there is an incomplete anatomic response, but relatively stable visual acuity and “treatment refractory” in which there is ongoing or increasing exudation and progressive visual decline despite monthly anti-VEGF therapy.

Tachyphylaxis or Tolerance

The term tachyphylaxis is defined as a diminished therapeutic response to a drug following repeated administration over time and is one mechanism by which treatment resistance to anti-VEGF therapy could occur [10]. One study showed that 10 % (6/58) of eyes treated with bevacizumab developed treatment resistance after a median time of 100 weeks and a median of eight injections; high dose intravitreal bevacizumab (2.50 mg) did not restore therapeutic response in these patients [11]. Eghøj and Sørensen [12] reported that 2 % of 976 patients developed tachyphylaxis over a period of 2 years of an OCT-guided intravitreal ranibizumab therapy. Factors that may play a role in the development of tachyphylaxis are drug administration frequency, dose, and the presence of antibodies targeting the drug. Even though both ranibizumab and bevacizumab are humanized monoclonal antibodies, they may be immunogenic. Another possible explanation for tachyphylaxis is the desensitization of the target tissue caused by up-regulation of VEGF receptors.

In addition to tachyphylaxis, treatment resistance could result from changes occurring in neovascular tissue itself including increased fibrosis, the development of polypoidal vasculopathy [13], and maturation of the vascular tissue making it less responsive to anti-VEGF [14•]. Changes occurring in the neighboring RPE and photoreceptors could also modulate the response to anti-VEGF. Other possible mechanisms of treatment resistance include increased VEGF expression related to macrophages within the neovascular lesion, or a shift of the biological pathway signal transduction towards other stimuli and growth factors involved in CNV growth. Several other pro-angiogenic signaling pathways could compensate for blocking the VEGF signaling pathway.

Strategies for the Management of Treatment Resistant Neovascular AMD

When treating neovascular AMD with anti-VEGF therapy, treatment resistance may occur at the initiation of therapy, or, more commonly, it may develop over the course of treatment. When eyes with treatment-naïve neovascular AMD do not initially respond to monthly anti-VEGF therapy, one should consider masqueraders of AMD including acquired vitelliform lesions in which subretinal fluid can occur without CNV, central serous chorioretinopathy, and polypoidal choroidal vasculopathy (PCV). In some cases of treatment resistance, we find it helpful to examine the patient within 2–3 weeks of an anti-VEGF injection to confirm that there is at least some response to the drug that may not be apparent when the patient is examined 1 month after the prior anti-VEGF injection. Once alternative diagnoses have been excluded and some response to anti-VEGF therapy is documented, there are a variety of strategies used to manage these cases. The most common strategies for managing these cases may be divided into the following categories: increasing the dose of the same anti-VEGF agent, increasing the frequency of administration of anti-VEGF therapy, switching to a different anti-VEGF agent, and combining anti-VEGF therapy with another treatment modality, most commonly photodynamic therapy (PDT).

Increasing the Anti-VEGF Dose

The most commonly used doses for each of the anti-VEGF agents are 0.5 mg/0.05 ml for ranibizumab [1, 2], 2.0 mg/0.05 ml for aflibercept [8•], and 1.25 mg/0.05 ml for bevacizumab.

Forooghian et al. [11] reported lack of efficacy of increasing the dose of bevacizumab to 2.5 mg in eyes with neovascular AMD for eyes that had previously demonstrated a therapeutic effect in the same monthly interval and subsequently experienced loss of response to this drug. Our experience with higher doses of bevacizumab has been similarly disappointing. Also, an injection exceeding 1.25 mg of bevacizumab requires an injection volume in excess of 0.05 ml causing higher post-injection pressure spikes that we prefer to avoid due to concerns of long-term sustained elevations in intraocular pressure.

The finding in the MARINA and ANCHOR trials that the 0.5 mg/0.05 ml dose of ranibizumab appeared to give slightly better visual outcomes than the 0.3 mg/0.05 ml dose [1, 2] suggests that even higher doses of ranibizumab might be of value in the management of resistant neovascular AMD eyes. While the phase III, double-masked, multicenter, randomized, active treatment-controlled study of the efficacy and safety of 0.5 and 2.0 mg ranibizumab

administered monthly or on an as-needed basis in patients with subfoveal neovascular AMD (HARBOR) trial did not show better visual outcomes in treatment-naïve eyes receiving a 2.0 mg/0.05 ml monthly dose of ranibizumab compared to eyes receiving 0.5 mg/0.05 ml ranibizumab monthly [15], there could be a role for higher doses in treatment resistant eyes.

In order to explore the possibility that higher doses of ranibizumab might be beneficial in cases of treatment resistance, we initiated the LAST study (pilot study to evaluate the role of high-dose ranibizumab 2.0 mg in the management of neovascular AMD in patients with persistent/recurrent macular fluid <30 days following treatment with intravitreal anti-VEGF therapy) which compared the outcomes of 2.0 mg/0.05 ml and 0.5 mg/0.05 ml monthly ranibizumab in cases with persistent subretinal or intraretinal fluid following at least six monthly intravitreal injections of 0.5 mg ranibizumab or 1.25 mg bevacizumab [16]. Following three consecutive monthly treatments we used a “treat and extend” regimen (TER). At month 6, the mean improvement in BCVA was +6.1 letters and +2.0 ETDRS letters in the 2.0 and 0.5 mg groups, respectively. The 2.0 mg group achieved better anatomical outcomes with a significant decrease in SRF and maximum PED height. No adverse events were reported in either group.

Other investigators have tried higher doses of ranibizumab in treatment resistant eyes. Chan et al. [17] reported a series of three treatment-naïve cases with dramatic resolution of subretinal fluid and flattening of the PED following the first intravitreal injection of 2.0 mg ranibizumab. The SAVE (super-dose anti-VEGF) phase I–II multicenter, open-label, randomized, controlled clinical trial evaluated the efficacy of 2.0 mg ranibizumab in a volume of 0.05 ml (formulated by Genentech, Inc.) in cases with persistent activity despite monthly intravitreal ranibizumab and/or bevacizumab treatment [18]. These patients were treated with three consecutive monthly injections of 2.0 mg ranibizumab followed by a capped pro re nata (PRN) strategy with fixed quarterly injections. At 3 months, 6 % of eyes gained and 1 % of eyes lost 15 or more letters, with an overall mean gain of +3.3 letters; a statistically significant decrease in retinal thickness was also evidenced, with resolution of intraretinal and subretinal fluid in 50.0 and 69.8 % of cases, respectively. There were no significant ocular or systemic safety issues. Sarraf et al. [19] found an increased risk for RPE tear in patients treated with 2.0 mg ranibizumab (10.8 %) compared with 0.5 mg (2.7 %), although these were cases with PED height, surface area, and greatest linear diameter significantly greater than those that did not develop RPE tears.

Further studies are needed to assess the safety and efficacy high-dose 2.0 mg ranibizumab for the management of treatment resistant neovascular AMD, but,

unfortunately, Genentech, Inc. appears to have discontinued their 2.0 mg ranibizumab program. Currently, as with bevacizumab, higher doses of ranibizumab require injecting volumes exceeding 0.05 ml using the commercially available formulation. For this reason, in our practice, we avoid using higher doses of ranibizumab.

Increase Anti-VEGF Frequency

While monthly injections of ranibizumab are often considered the “gold standard” for the treatment of neovascular AMD [1, 2], a variety of alternative dosing strategies have emerged in an attempt to minimize the burden of monthly follow-up visits and intravitreal treatments in patients with neovascular AMD. The two most commonly used alternative regimens are “as needed” OCT-guided PRN treatment and an extended maintenance regimen known as “treat and extend” (TER). In a PRN strategy, patients are followed every month with visual acuity and imaging findings, in particular OCT. Whenever a patient shows vision loss, bleeding or subretinal or intraretinal fluid on OCT, an injection may be performed; however, in the absence of vision loss, blood or macular edema, the patient is not injected and is instructed to return the following month [4, 5•, 6, 7•, 20–22].

The TER approach implies treatment at each visit, but at less than monthly intervals as the follow-up monitoring visits are extended gradually to a maximum 8–12 weeks interval if there continues to be an absence of visual acuity loss and exudative signs on OCT [23–25, 26•, 27]. If an eye shows recurrent fluid, the interval is shortened. If with monthly treatment, fluid persists, there is a rationale to shorten the anti-VEGF injection interval even further.

Stewart et al. [28] reported a mathematical model comparing the time-dependent relative binding activities of ranibizumab and bevacizumab showing that a significant improvement in trough binding activity may be achieved with biweekly injections. For example, the trough activities of 1.25 mg bevacizumab given biweekly ranged from 6.29 to 6.66-fold higher than those for 1.25 mg bevacizumab given monthly. Also, with 0.5 mg ranibizumab given biweekly, the 28-day trough binding activity was 5.44-fold higher than the trough of monthly 2.0 mg ranibizumab. The 28-day trough binding activity of monthly 0.5 mg aflibercept resulted in a 457.42-fold higher than for monthly 0.5 mg ranibizumab, 21.03-fold higher than 0.5 mg ranibizumab given biweekly, and 114.35-fold higher monthly 2.0 mg ranibizumab. And it resulted in 14–57-fold higher than that for monthly 1.25 mg bevacizumab [28]. The authors concluded from this VEGF binding activity model that increasing the frequency of anti-VEGF therapy to every 14 days may be an attractive alternative for resistant neovascular AMD cases, but

obviously with a significant increase in the burden and costs of visits and treatments. The other possibility could be switching the treatment to aflibercept as it was shown to have a higher VEGF binding activity.

In our practice, we occasionally use shorter than 28-day injection intervals in treatment-resistant cases. Typically, we try this option in eyes showing increasing fluid despite monthly treatment with 2.0 mg aflibercept. In some cases, we have been able to use this strategy successfully to consolidate the neovascular tissue allowing for a subsequent extension back to a longer dosing interval. We have observed a higher rate of RPE tears in treatment resistant eyes harboring large elevated vascularized PEDs when they are switched to this more intense regimen.

Change of Anti-VEGF Agent

Monthly injections of 0.5 mg ranibizumab are often considered the “gold standard” for the treatment of neovascular AMD [1, 2]. While monthly 1.25 mg bevacizumab was shown to be non-inferior to monthly 0.5 mg ranibizumab in several large randomized clinical trials, eyes treated with bevacizumab tend to have more fluid, making this drug a less attractive alternative anti-VEGF agent for treatment resistant cases [4, 5•, 6, 7•]. There have been several reports describing the results of switching treatment resistant eyes from bevacizumab to ranibizumab. Stepien et al. [29] reported a small subset of patients with neovascular AMD switched from bevacizumab to ranibizumab therapy with no differences in visual outcomes or injection rates. However, Kent et al. [30] showed an initial significant improvement in vision and macular thickness in patients initially treated with bevacizumab, with further significant improvement when they were uniformly switched to ranibizumab at the time that it became publicly funded by the local government. In another study, Gasperini et al. [31] reported that 81 % of resistant neovascular AMD cases evidenced at least some response following switching from bevacizumab to ranibizumab, but similar improvements were seen in eyes switched from ranibizumab to bevacizumab, suggesting that tachyphylaxis to the prior agent was the mechanism for the improvements seen following the switch rather than a higher potency of ranibizumab.

Once aflibercept became commercially available, it became a popular choice for rescue therapy in eyes showing treatment resistance to bevacizumab and/or ranibizumab [27]. The reported higher binding affinity of aflibercept and mathematical modeling by Stewart et al. [28] showing higher trough VEGF binding activity for longer durations than the alternative agents, made aflibercept an attractive choice for this purpose. Although 2.0 mg aflibercept is approved as a bi-monthly treatment following

three monthly doses, the VIEW 1 and VIEW 2 studies showed that monthly 2.0 mg aflibercept had similar safety to monthly 0.5 mg ranibizumab and achieved superior visual outcomes to monthly 0.5 mg ranibizumab at 1 year in one of these large pivotal trials. These findings further support the use of monthly 2.0 mg aflibercept for treatment resistant eyes. Our practice's experience with this strategy was reported by Kumar et al. [32•] who showed positive visual and anatomical outcomes after 6 months of treatment with aflibercept in cases with persistent subretinal and/or intraretinal fluid despite monthly treatment with ranibizumab. The mean visual acuity improved from 20/75 to 20/60; the mean central foveal thickness decreased from 416 to 248 μm ; the mean maximum PED height decreased from 260 to 214 μm , and the mean PED diameter decreased from 3.3 to 2.9 [32•]. Following this publication, several retrospective case series have shown a variable efficacy of switching eyes from ranibizumab and/or bevacizumab to aflibercept. The majority of these reports show considerable variability in the definition of treatment resistance, length of follow-up, and the anti-VEGF treatment regimens prior to the switch to aflibercept.

Patel et al. [33] reported a dramatic resolution and visual improvement in eyes with large serous PEDs and subretinal fluid associated with occult neovascular AMD following intravitreal administration of aflibercept over a 3-month period after bevacizumab and/or ranibizumab failed to resolve these lesions.

Ho et al. [34] evaluated the response to switching 96 eyes in 85 patients from bevacizumab, ranibizumab or both to three monthly consecutive aflibercept injections followed by an additional injection 2 months later. By month 4 ± 1 , 86 % of eyes remained stable (± 1 line of vision), 7 % gained two or more lines, and 7 % lost two or more lines. The qualitative analysis of OCT morphology showed complete resolution of exudation in 5 %, partial resolution in 49 %, no change in 32 %, and worsening in 14 %.

Yonekawa et al. [35] evaluated the response to switching 102 eyes of 94 patients from bevacizumab and/or ranibizumab to aflibercept. After a mean follow-up of 18 weeks and 3.8 aflibercept injections, the mean central macular thickness significantly decreased and the injection interval was extended from 5.2 to 6.2 weeks with aflibercept in refractory cases (persistent exudation) and from 7.2 to 9.5 weeks in recurrent cases (exudation suppressed but requiring frequent retreatments). However, there was no significant improvement in visual acuity.

Bakall et al. [36] evaluated the response to switching 36 eyes in 31 patients from bevacizumab and/or ranibizumab to three consecutive monthly aflibercept injections. Subretinal or intraretinal fluid decreased in 50 %, remained stable in 41.7 %, and increased in 8.3 %. However, no significant improvement in visual acuity was observed.

Cho et al. [37] evaluated the response to switching 28 eyes in 28 patients from bevacizumab and/or ranibizumab to monthly aflibercept, although 75 % of cases were extended to 6–8 week treatment intervals within the 6-month study period. After an average of 4.4 aflibercept injections, 64 % of eyes with persistent subretinal fluid had some degree of improvement, 23 % remained stable, and 14 % worsened. Of those with persistent intraretinal fluid, 63 % showed improvement, 25 % remained stable, and 13 % worsened. 47 % of eyes with PED had some improvement in its height, 53 % remained stable, and none got worse. However, no significant improvement in visual acuity was observed.

Combination Therapies

The rationale for combining different therapeutic approaches for the management of neovascular AMD relates to the diversity of neovascular lesion types and the different biochemical pathways that can lead to CNV formation and activity. One of the most frequently used combination approaches for neovascular AMD has been verteporfin PDT combined with intravitreal anti-VEGF therapy. In general, for treatment naïve eyes, PDT combined with anti-VEGF therapy may reduce the need for frequent injections, but may not achieve equivalent visual acuity outcomes [1–3]. Indeed, randomized trials comparing PDT and ranibizumab to ranibizumab alone showed that ranibizumab monotherapy yielded superior visual outcomes [38, 39]. However, in certain situations, such as treatment resistant cases and PCV, verteporfin PDT combined with anti-VEGF therapy may be useful. In the EVEREST Study, although no difference was seen in visual outcomes, verteporfin PDT combined with anti-VEGF therapy achieved a higher rate of polyp closure when compared to anti-VEGF monotherapy [40].

It has been suggested that combining an intravitreal steroid with anti-VEGF therapy may be beneficial by inhibiting the underlying inflammatory component of CNV [41, 42]. Veurink et al. [43] evaluated the in vitro stability of ranibizumab and bevacizumab in combination with dexamethasone phosphate and triamcinolone acetonide, showing that the resulting suspension might not decrease the stability of these antibodies.

Schaal et al. [44] suggested that the combination of preservative-free triamcinolone acetonide may reduce the bioefficacy of intravitreal bevacizumab monotherapy in cases of neovascular AMD. A few other reports have suggested a possible role of dexamethasone in combination with anti-VEGF therapies [45, 46]. Studies exploring the combination of verteporfin PDT, anti-VEGF and intravitreal dexamethasone failed to show superior visual outcomes when compared to anti-VEGF monotherapy [47–49].

In our practice, we use the combination of PDT and anti-VEGF in managing select cases of treatment resistance when the other strategies described above have failed. We have had the greatest success using PDT and anti-VEGF combination therapy in eyes in which the continued exudation can be attributed to PCV and in eyes having with overlapping features of neovascular AMD and CSC. We are not currently using combination strategies employing intravitreal steroids, as we have not found the addition of either intravitreal dexamethasone or triamcinolone acetonide to be of added benefit.

Conclusions

Clinical Pearls for the Management of Treatment Resistant Neovascular AMD

It is not possible to summarize our current approach to managing eyes exhibiting treatment resistance, as individualized therapy is currently the trend in our practice. We tend to modify our regimen primarily in eyes in which persistent exudation is associated with vision decline, those we describe as “treatment refractory.” For these eyes, if they are currently on monthly bevacizumab or ranibizumab, we will frequently switch to monthly aflibercept as our initial approach. Often, this switch will result in an improved anatomic appearance, sometimes with a small incremental improvement in visual acuity [32]. In our experience, aflibercept appears more effective than the alternative agents in eyes with PCV, particularly when there is concomitant increased choroidal thickness. We have observed a high frequency of treatment resistance in eyes having features of both neovascular AMD and CSC, an entity we call “pachychoroid neovascularopathy” [50].

If fluid persists following a switch to monthly aflibercept, we will sometimes perform a brief trial of bi-monthly anti-VEGF therapy that usually involves an injection of bevacizumab given midway between monthly aflibercept injections. In some eyes, this strategy has resulted in consolidation of the neovascular tissue manifested as flattening of vascularized PEDs on OCT. When this occurs, we have sometimes been able to maintain stability in these eyes with less frequent injections.

We tend to use verteporfin PDT in combination with anti-VEGF therapy in those cases in which these other strategies have failed and there is ongoing vision loss or when imaging clearly shows PCV as the cause of treatment resistance. When performing combined PDT and anti-VEGF therapy, we typically use half-fluence PDT (full-fluence for PCV) in between monthly anti-VEGF treatments. We typically treat the smallest area possible in hope

of reducing the risk of severe vision loss and, if feasible, direct foveal treatment.

In summary, the management of treatment resistance is one of the greatest challenges we face when treating neovascular AMD. While there are multiple strategies to choose from, there is little randomized clinical trial data to help guide the decision as to which of these options to choose. For these patients, clinicians may be best-served by drawing from their own experience, using good clinical judgment, and recognizing that neovascular AMD is a chronic disease which requires long-term management.

Acknowledgment Supported by the Macula Foundation, Inc., New York, NY.

Disclosure Dr. K. Bailey Freund, Dr. Sarah Mrejen, and Dr. Roberto Gallego-Pinazo claim they do not have a proprietary interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY, MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419–31.
2. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S, ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1432–44.
3. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T, ANCHOR Study Group. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. *Ophthalmology*. 2009;116:57–65.e5.
4. CATT Research Group, 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;364:1897–908.
5. •• Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group; Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, Toth C, Redford M, Ferris FL III. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012;119:1388–98. *The CATT trial (1185 patients) demonstrated that the 2-year visual outcomes of treatment with ranibizumab and bevacizumab were similar in the study groups receiving monthly injections, but with more serious systemic adverse events in patients treated with bevacizumab than with ranibizumab (adjusted risk ratio: 1.30).*
6. IVAN Study Investigators, Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, Reeves BC. Ranibizumab versus bevacizumab to treat neovascular age-related

- macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology*. 2012;119:1399–411.
7. •• Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Culliford LA, Reeves BC; on behalf of the IVAN Study Investigators. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet*. 2013. doi:10.1016/S0140-6736(13)61501-9. *The IVAN trial (525 patients) failed to show any statistically significant differences in visual outcomes, ocular safety and systemic safety in patients randomized to treatment with either ranibizumab or bevacizumab.*
 8. •• Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, Kirchhof B, Ho A, Ogura Y, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Soo Y, Anderesi M, Groetzsch G, Sommerauer B, Sandbrink R, Simader C, Schmidt-Erfurth U; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119:2537–48. *The VIEW 1 and VIEW 2 trials (2419 patients) showed that, at one year, aflibercept given bimonthly was non- and clinically equivalent to ranibizumab given monthly. The ocular and systemic safeties of aflibercept were similar to that of ranibizumab.*
 9. • Rofagha S, Bhisitkul RB, Boyer DS, Sadda SR, Zhang K; SEVEN-UP Study Group. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). *Ophthalmology*. 2013. doi:10.1016/j.ophtha.2013.03.046. *The evaluation of a cohort of 65 patients approximately 7 years after their enrollment in the ANCHOR and MARINA trials showed that 1/3 of cases achieved good visual outcomes, whereas 1/3 had substantial visual decline.*
 10. Binder S. Loss of reactivity in intravitreal anti-VEGF therapy: tachyphylaxis or tolerance? *Br J Ophthalmol*. 2012;96:1–2.
 11. Forooghian F, Cukras C, Meyerle CB, Chew EY, Wong WT. Tachyphylaxis after intravitreal bevacizumab for exudative age-related macular degeneration. *Retina*. 2009;29:723–31.
 12. Eghøj MS, Sørensen TL. Tachyphylaxis during treatment of exudative age-related macular degeneration with ranibizumab. *Br J Ophthalmol*. 2012;96:21–3.
 13. Cho M, Barbazetto IA, Freund KB. Refractory neovascular age-related macular degeneration secondary to polypoidal choroidal vasculopathy. *Am J Ophthalmol*. 2009;148:70–8.e1.
 14. • Shah VP, Freund KB. Growth of type 1 neovascularization following cessation of anti-vascular endothelial growth factor therapy as a possible explanation for treatment resistance. *JAMA Ophthalmol*. 2013;131:967–9. *Case report showing that interrupted VEGF inhibition may lead to growth and maturation of type 1 neovascularization and refractory exudation due to resistant neovascular tissue.*
 15. Busbee BG, Ho AC, Brown DM, Heier JS, Suñer IJ, Li Z, Rubio RG, Lai P, HARBOR Study Group. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2013;120:1046–56.
 16. Fung AT, Kumar N, Vance SK, Slakter JS, Klancnik JM, Spaide RS, Freund KB. 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 (Lond.)*. 2012;26:1181–7.
 17. Chan CK, Abraham P, Sarraf D. High-dose ranibizumab therapy for vascularized pigment epithelial detachment. *Eye (Lond.)*. 2012;26:882–5.
 18. Brown DM, Chen E, Mariani A, Major JC Jr, SAVE Study Group. Super-dose anti-VEGF (SAVE) trial: 2.0 mg intravitreal ranibizumab for recalcitrant neovascular macular degeneration—primary end point. *Ophthalmology*. 2013;120:349–54.
 19. Sarraf D, Chan C, Rahimy E, Abraham P. Prospective evaluation of the incidence and risk factors for the development of RPE tears after high- and low-dose ranibizumab therapy. *Retina*. 2013;33:1551–7.
 20. Fung AE, Lalwani GA, Rosenfeld PJ, Dubovy SR, Michels S, Feuer WJ, Puliafito CA, Davis JL, Flynn HW Jr, Esquiabro M. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol*. 2007;143:566–83.
 21. Holz FG, Amoaku W, Donate J, Guymer RH, Kellner U, Schlingemann RO, Weichselberger A, Staurengi G, SUSTAIN Study Group. Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study. *Ophthalmology*. 2011;118:663–71.
 22. Lalwani GA, Rosenfeld PJ, Fung AE, Dubovy SR, Michels S, Feuer W, Davis JL, Flynn HW Jr, Esquiabro M. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. *Am J Ophthalmol*. 2009;148:43–58.e1.
 23. Engelbert M, Zweifel SA, Freund KB. “Treat and extend” dosing of intravitreal antivascular endothelial growth factor therapy for type 3 neovascularization/retinal angiomatous proliferation. *Retina*. 2009;29:1424–31.
 24. Engelbert M, Zweifel SA, Freund KB. Long-term follow-up for type 1 (subretinal pigment epithelium) neovascularization using a modified “treat and extend” dosing regimen of intravitreal antivascular endothelial growth factor therapy. *Retina*. 2010;30:1368–75.
 25. Gupta OP, Shienbaum G, Patel AH, Fecarotta C, Kaiser RS, Regillo CD. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact. *Ophthalmology*. 2010;117:2134–40.
 26. • Oubraham H, Cohen SY, Samimi S, Marotte D, Bouzahr I, Bonicel P, Fajnkuchen F, Tadayoni R. Inject and extend dosing versus dosing as needed: a comparative retrospective study of ranibizumab in exudative age-related macular degeneration. *Retina*. 2011;31:26–30. *This comparative study of as-needed and treat and extend anti-VEGF dosing regimens showed that patients treated with the treat and extend dosing regimen had better visual outcomes, but received more injections.*
 27. Freund KB, Mrejen S, Gallego-Pinazo R. An update on the pharmacotherapy of neovascular age-related macular degeneration. *Expert Opin Pharmacother*. 2013;14:1017–28.
 28. Stewart MW, Rosenfeld PJ, Penha FM, Wang F, Yehoshua Z, Bueno-Lopez E, Lopez PF. Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor Trap-eye). *Retina*. 2012;32:434–57.
 29. Stepien KE, Rosenfeld PJ, Puliafito CA, Feuer W, Shi W, Al-Attar L, Dubovy SR, Murray TG, Davis JL, Lee WH, Schwartz SG, Smiddy WE, Berrocal AM, Flynn HW Jr. Comparison of intravitreal bevacizumab followed by ranibizumab for the treatment of neovascular age-related macular degeneration. *Retina*. 2009;29:1067–73.
 30. Kent JS, Iordanous Y, Mao A, Powell AM, Kent SS, Sheidow TG. Comparison of outcomes after switching treatment from intravitreal bevacizumab to ranibizumab in neovascular age-related macular degeneration. *Can J Ophthalmol*. 2012;47:159–64.
 31. Gasperini JL, Fawzi AA, Khondkaryan A, Lam L, Chong LP, Elliott D, Walsh AC, Hwang J, Sadda SR. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation. *Br J Ophthalmol*. 2012;96:14–20.
 32. •• Kumar N, Marsiglia M, Mrejen S, Fung AT, Slakter J, Sorenson J, Freund KB. Visual and anatomical outcomes of

- intravitreal aflibercept in eyes with persistent subfoveal fluid despite previous treatments with ranibizumab in patients with neovascular age-related macular degeneration. *Retina*. 2013;33:1605–12. *A cohort of 33 eyes with persistent subretinal and/or intraretinal fluid despite treatment with intravitreal ranibizumab was treated with intravitreal aflibercept and showed significant visual and anatomical improvements.*
33. Patel KH, Chow CC, Rathod R, Mieler WF, Lim JJ, Ulanski LJ II, Leiderman YI, Arun V, Chau FY. Rapid response of retinal pigment epithelial detachments to intravitreal aflibercept in neovascular age-related macular degeneration refractory to bevacizumab and ranibizumab. *Eye (Lond.)*. 2013;27:663–7.
 34. Ho VY, Yeh S, Olsen TW, Bergstrom CS, Yan J, Cribbs BE, Hubbard GB III. Short-term outcomes of aflibercept for neovascular age-related macular degeneration in eyes previously treated with other vascular endothelial growth factor inhibitors. *Am J Ophthalmol*. 2013;156:23–8.e2.
 35. Yonekawa Y, Andreoli C, Miller JB, Loewenstein JJ, Sobrin L, Elliott D, Vavvas DG, Miller JW, Kim IK. Conversion to aflibercept for chronic refractory or recurrent neovascular age-related macular degeneration. *Am J Ophthalmol*. 2013;156:29–35.e2.
 36. Bakall B, Folk JC, Boldt HC, Sohn EH, Stone EM, Russell SR, Mahajan VB. Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab. *Am J Ophthalmol*. 2013;156:15–22.e1.
 37. Cho H, Shah CP, Weber M, Heier JS. Aflibercept for exudative AMD with persistent fluid on ranibizumab and/or bevacizumab. *Br J Ophthalmol*. 2013;97:1032–5.
 38. Kaiser PK, Boyer DS, Cruess AF, Slakter JS, Pilz S, Weisberger A, DENALI Study Group. Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study. *Ophthalmology*. 2012;119:1001–10.
 39. Larsen M, Schmidt-Erfurth U, Lanzetta P, Wolf S, Simader C, Tokaji E, Pilz S, Weisberger A, MONT BLANC Study Group. Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results. *Ophthalmology*. 2012;119:992–1000.
 40. Koh A, Lee WK, Chen LJ, Chen SJ, Hashad Y, Kim H, Lai TY, Pilz S, Ruamviboonsuk P, Tokaji E, Weisberger A, Lim TH. EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina*. 2012;32:1453–64.
 41. Edelman JL, Lutz D, Castro MR. Corticosteroids inhibit VEGF-induced vascular leakage in a rabbit model of blood-retinal and blood-aqueous barrier breakdown. *Exp Eye Res*. 2005;80:249–58.
 42. Wenzel A, Grimm C, Seeliger MW, Jaissle G, Hafezi F, Kretschmer R, Zrenner E, Remé CE. Prevention of photoreceptor apoptosis by activation of the glucocorticoid receptor. *Investig Ophthalmol Vis Sci*. 2001;42:1653–9.
 43. Veurink M, Stella C, Tabatabay C, Pournaras CJ, Gurny R. Association of ranibizumab (Lucentis®) or bevacizumab (Avastin®) with dexamethasone and triamcinolone acetonide: an in vitro stability assessment. *Eur J Pharm Biopharm*. 2011;78:271–7.
 44. Schaal S, Kaplan HJ, Tezel TH. Is there tachyphylaxis to intravitreal anti-vascular endothelial growth factor pharmacotherapy in age-related macular degeneration? *Ophthalmology*. 2008;115:2199–205.
 45. Ranchod TM, Ray SK, Daniels SA, Leong CJ, Ting TD, Verne AZ. LUCEDEX: a prospective study comparing ranibizumab plus dexamethasone combination therapy versus ranibizumab monotherapy for neovascular age-related macular degeneration. *Retina*. 2013;33:1600–4.
 46. Gallego-Pinazo R, Marín-Lambies C, Marín-Olmos F, Martínez R, Fons R, Díaz-Llopis M. Intravitreal dexamethasone as an enhancer for the anti-VEGF treatment in neovascular ARMD: recovering an old ally. *Arch Soc Esp Oftalmol*. 2010;85:79–80.
 47. Forte R, Bonavolontà P, Benayoun Y, Adenis JP, Robert PY. Intravitreal ranibizumab and bevacizumab in combination with full-fluence verteporfin therapy and dexamethasone for exudative age-related macular degeneration. *Ophthalmic Res*. 2011;45:129–34.
 48. Bakri SJ, Couch SM, McCannel CA, Edwards AO. Same-day triple therapy with photodynamic therapy, intravitreal dexamethasone, and bevacizumab in wet age-related macular degeneration. *Retina*. 2009;29:573–8.
 49. Augustin AJ, Puls S, Offermann I. Triple therapy for choroidal neovascularization due to age-related macular degeneration: verteporfin PDT, bevacizumab, and dexamethasone. *Retina*. 2007;27:133–40.
 50. • Warrow DJ, Hoang QV, Freund KB. Pachychoroid pigment epitheliopathy. *Retina*. 2013;33:1659–72. *This observational case series of 9 patients describes a new entity called “pachychoroid pigment epitheliopathy” in which retinal pigment epithelium abnormalities are seen in association with choroidal thickening and dilated choroidal vessels but without a history of subretinal fluid.*