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Treatment Paradigms in Neovascular AMD

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Abstract Age-related macular degeneration (AMD) affects more than 7 million individuals in the USA, making it the most common cause of visual impairment among adults over 60 years of age. Although the precise mechanisms responsible for the development of AMD are not fully understood, it is well established that vascular endothelial growth factor (VEGF) plays a major role in the development and growth of the choroidal neovascular membrane. Anti-VEGF treatment has become the corner stone of management of this condition. In this article we discuss the current evidence for the various treatment paradigms presently in practical use, including the frequency of anti-VEGF injections as well as the use of combination treatments.

Keywords Neovascular AMD · Anti-VEGF · Treatment paradigms · Combination treatment · Triple therapy · PEDF inhibitors · Radiation

Introduction

Epidemiology and Pathogenesis

Age-related macular degeneration (AMD) affects more than 7 million individuals in the USA, making it the most common cause of visual impairment among adults over 60 years of age. The prevalence of AMD varies according to the population studied, estimated at 15 % of white women compared to 2.44 % of African American older than 80 years. Recently, 60-year-old Asian Americans were found to have a 28 % higher risk for AMD than similarly aged white Americans [1]. The 10-year cumulative incidence of neovascular AMD in the Blue Mountains Eye Study population was 2.2 % for individuals aged 49 years and older at baseline, increasing from 2.0 % for individuals aged 60–69 years at baseline to 12.4 % for those aged 80 years and older [2]. Moreover, population projections estimate a substantial increase in the older populations resulting in a further increase in the morbidity of the disease [3, 4].

AMD pathogenesis is likely multifactorial and polygenetic. Age and family history were shown to be non-modifiable risk factors of AMD [5]. Epidemiologic data demonstrated a relationship between AMD and complement factor H [6], as well as with excision repair cross-complementing rodent repair deficiency complementation group 6, involved in DNA repair [7]. In addition, systemic conditions such as hypertension and atherosclerosis, and environmental exposure such as smoking have been shown to be a risk factor for the development of neovascular AMD [8, 9]. Neovascular AMD is characterized by the development of a choroidal neovascular membrane (CNVM). Long-standing oxidative stress and the resultant tissue inflammation underlie the pathogenesis and progression of CNVM [10, 11]. Drusen are composed of pro-inflammatory components such as complement, C reactive protein, and advanced glycation end product, as such they are thought to be one of the main indicators of increased risk for developing CNVM by triggering local inflammation.

Current Treatment Modalities

Although the precise mechanisms responsible for the development of AMD are not fully understood, it is well established that vascular endothelial growth factor (VEGF)

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plays a major role in the development and growth of the CNVM [12]. Anti-VEGF treatment has become the corner stone of management of this condition.

Pharmacology and Pharmacokinetics

Therapeutic agents targeting VEGF inhibit the functional pathway by binding to either VEGF or its receptors.

Pegaptanib (Macugen) is an aptamer, a short RNA oligonucleotide that assumes a specific three-dimensional shape and binds with high specificity and affinity to the major soluble human VEGF isoform. VEGF165 [13]. Bevacizumab (Avastin) and ranibizumab (Lucentis) are the two monoclonal antibody-derived therapies that are currently used in the treatment of wet AMD. Bevacizumab is a full-length recombinant humanized monoclonal antibody against VEGF-A. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF-A, and has a molecular weight of approximately 149 kDa. Ranibizumab is a monoclonal antibody fragment (Fab) derived from the same parent mouse antibody as bevacizumab. It is much smaller than the parent molecule and has been affinity matured to provide stronger binding to VEGF-A. It has a molecular weight of approximately 48 kDa [14, 15]. In human non-vitrectomized eyes, the concentration of 1.5 mg intravitreally administered bevacizumab peaked in the aqueous humour on the first day after injection, with a half-life of 9.82 days [16].

Aflibercept (Eylea) is a recombinant fusion protein, consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1. It binds VEGF-A and placental growth factor. Aflibercept was engineered to have optimized pharmacokinetic properties and a very high binding affinity for VEGF and longer half-life in the eye [17].

Efficacy of VEGF Inhibitors

Multiple multicenter, randomized, double-blind, Phase III clinical trials provide Level I evidence that patients treated with VEGF inhibitors have significant improvements in visual acuity (VA). For example, in the MARINA Study, a randomized, double-masked clinical trial in which patients with AMD were randomized 1:1:1 to monthly intravitreal Ranibizumab (0.3 or 0.5 mg) or sham injections. At the 2-year follow-up, the mean increases in VA were 6.5 letters in the 0.3-mg group and 7.2 letters in the 0.5-mg group, as compared with a decrease of 10.4 letters in the sham-injection group [18–23]. Similarly, in the ANCHOR trial, which compared ranibizumab injection (0.3 or 0.5 mg) to PDT, at month 24, VA had improved from baseline by 8.1 letters in the 0.3-mg group and 10.7 letters in the 0.5-mg group, compared with a mean decline of 9.8 letters in the PDT group.

Bevacizumab was shown to have a similar effect when compared to ranibizumab, In the recently published results of the Comparison of AMD Treatment Trials (CATTs), the first head-to-head comparison of ranibizumab versus bevacizumab, showed ranibizumab and bevacizumab had similar effects on VA over a 2-year period [24, 25•]. Among patients following the same regimen for 2 years, mean gain in VA was similar for both drugs (bevacizumab − ranibizumab difference, −1.4 letters; $P = 0.21$). Mean gain was greater for monthly than for as-needed treatment (difference, −2.4 letters; $P = 0.046$). The proportion without fluid ranged from 13.9 % in the bevacizumab-as-needed group to 45.5 % in the ranibizumab-monthly group (drug, $P = 0.0003$; regimen, $P < 0.0001$). Switching from monthly to as-needed treatment resulted in greater mean decrease in vision during year 2 (−2.2 letters; $P = 0.03$) and a lower proportion without fluid (−19 %; $P < 0.0001$). Rates of death and arteriothrombotic events were similar for both drugs ($P > 0.60$).

The VEGF-trap, aflibercept, studies have showed similar effects. Two parallel, Phase III, double-masked, randomized, multicenter studies evaluated the safety and efficacy of repeated dosing of aflibercept compared with the gold standard, ranibizumab: VIEW 1 (VEGF trap-eye: investigation of efficacy and safety in wet AMD) and VIEW 2. At 52 weeks, the VIEW 1 Study showed that in the aflibercept groups, vision was maintained in 96 % of patients receiving 0.5 mg monthly, 95 % of patients receiving 2 mg monthly and 95 % of patients receiving 2 mg every 2 months. In the group receiving ranibizumab 0.5 mg monthly, 94 % of patients maintained vision. VIEW 2 had similar results. In the aflibercept groups, vision was maintained in 96 % of patients receiving 0.5 mg monthly, 96 % of patients receiving 2 mg monthly and 96 % of patients receiving 2 mg every 2 months. In the group receiving ranibizumab 0.5 mg monthly, 94 % of patients maintained vision [26, 27].

Treatment Paradigms

Monthly Treatments

To date, anti-VEGF treatment has been shown to be a safe and effective treatment for patients with all subtypes of neovascular AMD. The initial studies, which lead to the FDA approval of this therapy, were based on monthly injection of the agent. In addition, these studies confirmed that intravitreal ranibizumab was safe and well tolerated in a large population of subjects with neovascular AMD.

The MARINA and ANCHOR trials evaluated the efficacy and safety of monthly ranibizumab (0.3 or 0.5 mg) versus sham injection (MARINA) and versus PDT with verteporfin (ANCHOR). In both trials, patients treated with

ranibizumab had significant improvements in VA at 12 and 24 months [18, 19]. The ANCHOR trial was able to demonstrate that ranibizumab administered as monthly intravitreal injections of 0.3 or 0.5 mg over a 24-month period was effective, and superior to PDT treatment, in maintaining or improving VA and lesion characteristics in patients with predominantly classic subfoveal neovascular AMD. While the ANCHOR trial investigated efficacy of ranibizumab only in predominantly classic CNV, the MARINA Study evaluated the efficacy of ranibizumab in non-classic (minimally classic and occult) CNVM.

In the ANCHOR trial, at 12 months, mean VA increased by 11.3 letters in the 0.5 mg ranibizumab group whereas in the verteporfin group it decreased by 9.5 letters ($P < 0.001$). At 24 months, mean VA improved by 10.7 letters in the 0.5 mg ranibizumab group, but decreased by 9.8 letters in the verteporfin group. At months 12 and 24, ranibizumab was superior to PDT ($P < 0.0001$) for mean changes in baseline in total area of lesion, CNVM area, and total area CNVM leakage [19, 28–30].

The MARINA trial showed similar results, patients treated with 0.3 or 0.5 mg ranibizumab gained, respectively, 6.5 and 7.2 letters from baseline to 1 year, whereas the sham-injection group lost 10.4 letters ($P < 0.0001$). At 24 months, patients in the 0.5 mg ranibizumab group gained 6.6 letters, compared with a mean loss of 14.9 letters in the sham-injection group ($P < 0.001$) [18].

In the HORIZON Study, patients who had previously completed 24-month treatment with monthly injections of ranibizumab as participants in FOCUS, MARINA or ANCHOR trials were evaluated for 2 years in an open-label extension study. In this study, patients could receive intravitreal injection of 0.5 mg ranibizumab at the discretion of the investigator as often as every month in the study eye. There were three treatment groups; the treated-initial group ($n = 600$) composed of the patients who received ranibizumab 0.3, 0.5 mg or ranibizumab 0.5 mg plus verteporfin photodynamic therapy, the treated-crossover group ($n = 184$), in which patients who were assigned to sham group in the initial study and received ranibizumab either in the initial study or in HORIZON Study, and the untreated group ($n = 69$); these patients were never treated with ranibizumab either in the original study or in HORIZON Study. Of the 853 patients enrolled in HORIZON Study, 573 patients received ranibizumab through year 2, with a mean 3.6 injections in treated-initial group, and 4.2 injections in treated-crossover group. 32 % in treated-initial, and 12 % in treated-crossover group did not receive any injections. Among treated-initial group, gain of 10.2 letters from initial baseline decreased to an overall gain of 5.1 letters (loss of 5.1 letters from the time of entry into HORIZON) at 1 year in HORIZON and decreased further to a total gain of 2 letters at year 2 in HORIZON. Patients in treated-crossover groups lost an additional 2 letters at year 2 in HORIZON Study, and those who never received Ranibizumab lost an additional 3.7 letters. The HORIZON Study showed that the visual gain achieved after 2 years of monthly injections was not maintained with less frequent dosing of ranibizumab [31•].

More recently, the results of the CATT and IVAN trials showed that ranibizumab and bevacizumab had similar effects on VA. In the CATT trial at the end of year 1, bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. At 2 years, the mean increase in VA from baseline was 8.8 in the ranibizumab-monthly group, 7.8 in the bevacizumab monthly group [24, 25•]. Similarly, the 1 year findings of the IVAN Study showed a mean difference between the drugs of two letters in favor of ranibizumab, when both drugs were injected on a monthly basis [32].

These studies all showed that the most significant visual gain occurred in the first 3 months with stabilization over the next 21 months. Following the MARINA and ANCHOR trials, several studies looked at ways to decrease the treatment burden while maintaining similar visual gains.

Quarterly versus Monthly versus As-Needed

The PIER trial evaluated an alternative dosage regimen to the monthly injections for neovascular AMD. The 2-year trial was designed to determine the efficacy and safety of a modified dosage regimen consisting of intravitreal dosage every month for three doses, followed by an additional injection mandated every 3 months [20]. As seen in earlier studies, PIER demonstrated a VA benefit in the first 3 months compared to sham. The quarterly dosing schedule, however, showed a steady decline in VA during months 4 through 24 compared to the VA stabilization achieved in ANCHOR and MARINA with monthly ranibizumab injections [33].

The PrONTO Study is a 2-year, open-label, prospective, single-center, uncontrolled clinical study that was designed to investigate the efficacy, durability, and safety of a variable-dosing regimen with intravitreal ranibizumab in patients with neovascular AMD primarily guided by optical coherence tomography (OCT). Patients with CNVM involving the central fovea and central retinal thickness (CRT) of at least 300 μm or as measured by OCT were enrolled to receive three consecutive monthly intravitreal injections of 0.5 mg ranibizumab. After the first three monthly injections, retreatment with ranibizumab was performed at each subsequent monthly visit if any of the five different retreatment criteria was met: (i) VA loss of at least five letters with OCT evidence of fluid in the macula; (ii) an increase in OCT CRT of at least 100 μm; (iii) new macular hemorrhage; (iv) new area of classic CNV; or (v) evidence of persistent fluid on OCT 1 month after the

previous injection. During the second year, the retreatment criteria were amended to include retreatment if any qualitative increase in the amount of fluid was detected using OCT [34]. The use of an OCT-guided variable-dosing regimen with ranibizumab resulted in VA outcomes similar to results from the MARINA and ANCHOR studies while averaging 59 % less (9.9 vs. 24) injections over 2 years. While the PrONTO Study indicated that patients could be treated by need while maintaining good outcomes, the results of this study were limited by its small size, lack of a control group, and amendments to the retreatment criteria after 1 year. This led to the SUSTAIN trial, a large, multicenter trial that explored an individualized ranibizumab PRN treatment regimen [35•]. In this study, patient received monthly injections for 3 months, followed by PRN dosing according to retreatment criteria similar to, but less flexible than the PrONTO trial. The results of this trial showed that the initial improvement of +5.8 letters after 3 months was not maintained. This may be due to the retreatment criteria of this study. Since this study, other groups have published about their experience with "treat-and-extend" [36, 37] in an attempt to reduce the number of visits and injections while maintaining vision. In this method, patients are treated with three monthly injections and are then followed at 6 weeks and receive an injection. If at the 6-week visit, there is no evidence of disease activity, they are instructed to return in 8 weeks, if there are signs of activity, they are instructed to return in 4 weeks. Although this method is logical, there are no prospective studies supporting its efficacy.

CATT is the most recent landmark trial for neovascular AMD. In addition to comparing the safety and efficacy of two treatments, ranibizumab and bevacizumab, for subfoveal neovascular AMD, each arm of the study was randomized for monthly versus variable-dosing schedule based on signs of lesion activity. At enrollment, patients were assigned to four treatment groups defined by drug and dosing regimen. At 1 year, patients initially assigned to monthly treatment were reassigned randomly to monthly or as-needed treatment, without changing the drug assignment. The dose per intravitreal injection was 0.5 mg ranibizumab or 1.25 mg bevacizumab. Patients receiving the as-needed dosing regimen were evaluated for treatment every 4 weeks and were treated when fluid was present on OCT or when new or persistent hemorrhage, decreased VA relative to the previous visit, or dye leakage on fluorescein angiography was present. At the conclusion of the study only small differences in mean gain in VA emerged between dosing regimens. At 2 years, as-needed dosing of either drug produced 2.4 letters less mean gain than monthly dosing ($P = 0.046$), with the greatest difference (3.8 letters) between ranibizumab monthly and bevacizumab as-needed. The mean ± standard deviation number of injections through year 2 in the as-needed groups was 12.6 ± 6.6 for patients treated with ranibizumab and 14.1 ± 7.0 for those treated with bevacizumab. Of interest, the development of geographic atrophy was higher in both monthly treated groups than in the as-needed groups.

Confirming these findings, the recently published IVAN trial showed that there was no significant difference in VA between continuous and as-needed regimens, differing by only 0.35 letters [32].

The 2011 ASRS Preferences and Trends Survey, published prior to the results of year-2 CATT trial showed that 60 % of respondents continue to use a 'treat-and-extend' protocol when following their patients with wet AMD, compared to 32 % who follow monthly and treat when active. When asked of their current management of a 70-year-old patient with a subfoveal CNV lesion size 1 disc area, 20/100 VA, 70.63 % of respondents said they treated with Lucentis, while 26.94 % preferred Avastin.

In another survey question, 73.24 % reported that regardless of the CATT Study results, they continue using the same neovascular AMD treatment on existing patients they were using prior to the trial, whereas 7.3 % of respondents switched from Lucentis to Avastin. 15.57 % continued using Avastin exclusively, 3.16 % continued using Lucentis exclusively and less than 1 % switched from Avastin to Lucentis. Bilateral simultaneous anti-VEGF injections for wet AMD have grown in popularity as more retina specialists gain experience with the treatment and an increased number of patients require bilateral treatment. While only 27 % of respondents in 2008 said they perform bilateral simultaneous anti-VEGF injections, the 2011 survey saw a huge jump up to 55 % of respondents.

VEGF Trap

In the Phase III trials of VEGF trap, the efficacy of repeated dosing of aflibercept compared with the gold standard, ranibizumab. The VIEW 1 (VEGF trap-eye: investigation of efficacy and safety in wet AMD) Study enrolled 1,217 patients with wet AMD in the USA and Canada. The VIEW 2 Study enrolled 1,240 patients in the EU, Asia Pacific, Japan and Latin America. These studies were designed as non-inferiority studies comparing intravitreal aflibercept with ranibizumab. The primary end point of the studies was designed to compare the proportion of patients who maintained vision at 52 weeks (defined as a loss of fewer than 15 ETDRS [Early Treatment Diabetic Retinopathy Study] letters). Patients with subfoveal CNVM due to AMD were randomized into four groups. The first two groups received intravitreal injections of aflibercept at doses of either 0.5 mg (group 1) or 2 mg (group 2) every

4 weeks. Group 3 patients received 2 mg of aflibercept at 8-week intervals following three initial loading doses given monthly. These groups were compared against group 4 patients, the control group, who received 0.5 mg of ranibizumab every 4 weeks. At 52 weeks, the VIEW 1 Study showed that in the aflibercept groups, vision was maintained in 96 % of patients receiving 0.5 mg monthly, 95 % of patients receiving 2 mg monthly and 95 % of patients receiving 2 mg every 2 months. In the group receiving ranibizumab 0.5 mg monthly, 94 % of patients maintained vision [26]. VIEW 2 had similar results: in the aflibercept groups, vision was maintained in 96 % of patients receiving 0.5 mg monthly, 96 % of patients receiving 2 mg monthly and 96 % of patients receiving 2 mg every 2 months. In the group receiving ranibizumab 0.5 mg monthly, 94 % of patients maintained vision [27]. Both studies showed non-inferiority among all treatment groups and demonstrated excellent safety. The most interesting finding from these studies was that the group that was injected every 2 months after three loading doses showed similar efficacy as the monthly group with no loss of vision at 52 weeks. This regimen offers less frequent injections.

It is yet to be determined if the addition of aflibercept to our armamentarium will change the current practices based on these results. In my opinion, aflibercept is a useful addition to our practice as a tool to decrease the number of injections and office visits without jeopardizing their VA outcome.

Combination Treatment

Several trials evaluated combination therapies, including PDT, radiation treatment and steroids for wet AMD.

PDT and Anti-VEGF

The SUMMIT clinical trial program evaluated the efficacy and safety of verteporfin–PDT in combination with ranibizumab compared with ranibizumab monotherapy. As part of this program, both the MONT BLANC and DENALI studies (conducted in Europe and in the USA and Canada, respectively) enrolled patients with neovascular AMD, and the EVEREST Study (conducted in Asia) evaluated the combination therapy in patients with polypoidal choroidal vasculopathy.

The DENALI Study demonstrated non-inferiority of ranibizumab in combination with verteporfin–PDT versus ranibizumab monotherapy in patients with subfoveal CNVM secondary to AMD [38•]. In this 12-month study which included 286 patients, the mean BCVA change at month 12 was +5.3 and +4.4 letters with verteporfin ($n = 103$) or verteporfin ($n = 105$) plus ranibizumab, respectively, compared with +8.1 letters with ranibizumab monotherapy ($n = 110$; $P = 0.0666$; and; $P = 0.1178$; for combination regimens vs. monotherapy, respectively). Non-inferiority of either combination regimen to monthly ranibizumab monotherapy was not demonstrated (primary end point). A ranibizumab treatment-free interval of 3 months or longer was achieved in 92.6 and 83.5 % of the patients randomized to verteporfin or verteporfin plus ranibizumab groups, respectively, with a mean of 5.1 and 5.7 ranibizumab injections, respectively, and patients in the ranibizumab monotherapy arm received 10.5 injections. Safety and tolerability of all three regimens were similar to and consistent with previous studies in neovascular AMD. The number of ocular serious adverse events was low and occurred largely as single cases.

Currently, combination therapy is used in patients not responding to monotherapy with ranibizumab for idiopathic polypoidal choroidal vasculopathy in which sub-RPE polyps are identified on indocyanine green angiography.

Radiation Study Results

Radiation therapy is currently under investigation as another treatment modality in combination with anti-VEGF therapy for neovascular AMD. Radiation targets proliferating cells and, therefore, can selectively damage dividing cells. Currently two different approaches to radiation therapy in the treatment of neovascular AMD are being investigated: epimacular brachytherapy (VIDION; NeoVista Inc., Fremont, CA) and stereotactic radiosurgery (IRay system; Oraya Therapeutics Inc., Newark, CA). Because radiotherapy produces a delayed response on the CNVM, a combination approach with Anti-VEGF agents, will likely result in a faster and more complete recovery of VA. Currently there are two prospective, randomized, controlled trials in treatment-naive subjects (CABERNET) and in subjects already treated with anti-VEGF therapy (MERLOT) [39]. Recently published, the 3-year safety and VA outcomes associated with epimacular strontium 90 brachytherapy combined with intravitreal bevacizumab for the treatment of subfoveal neovascular AMD in 34 treatment naïve patients has shown that this is a promising therapeutic option. Mean best-corrected VA demonstrated an average gain of +15.0 and −4.9 letters at 12 and 24 months, respectively; the drop in mean gain at month 24 was largely attributable to cataract formation. At 36 months ($n = 19$), the mean best-corrected VA was +3.9, 90 % (17 of 19) of eyes had lost <15 letters from baseline, 53 % (10 of 19) had gained >1 letter, and 21 % (4 of 19) had gained >15 letters. Through 36 months, 11 eyes required additional bevacizumab retreatment therapy and received a mean of 3.0 injections.

In the Phase I trial of the IRay system, non-invasive, low-voltage 16 Gray (Gy) X-ray irradiation delivered in three beams via the inferior pars plana in patients with

active neovascular AMD. Ranibizumab was administered as-needed per protocol. Patients were followed monthly for safety and efficacy over 12 months. The Phase I trial results demonstrated good safety with a stabilizing effect on VA and reduction in retinal thickness. 11 patients lost <15 letters, seven gained ≥0 ETDRS letters and 0 gained ≥15 ETDRS letters. Patients received a total of 31 subsequent Ranibizumab injections [40•].

The recently published 1-year results of the INTREPID (IRay Plus Anti-VEGF Treatment For Patients With Wet AMD) trial showed promising results. The INTREPID Study is a sham-controlled double-masked trial that evaluated the safety and efficacy of a one-time radiation therapy in conjunction with as-needed anti-VEGF injections for the treatment of wet AMD. All study patients had previously received at least three anti-VEGF injections in the prior year and required further anti-VEGF treatment. Within 2 weeks following injection, one-third of the subjects received a sham exposure and the remainder received a radiation dose of either 16 or 24 Gy. According to the recent press release, the study has met its primary end point of reduction in anti-VEGF injections in these patients. The preliminary analyses also found no indication of radiation-related adverse events at the 1-year end point [41, 42].

Pigment Epithelium-Derived Factor (PEDF) Inhibitors

PEDF is a potent anti-angiogenic factor. The Phase I trial results of a single intravitreous injection of an adenoviral vector expressing human PEDF (AdPEDF.11) have shown to have no serious adverse events or dose-limiting toxicity in patients with neovascular AMD. The data also suggested that the anti-angiogenic activity may last for several months after a single intravitreous injection. Therefore, when this agent becomes commercially available, combination with anti-VEGF therapy may reduce the need for monthly injections.

Recently, in a prospective, randomized, controlled Phase IIb clinical trial of patients with neovascular AMD, anti-PDGF therapy (1.5 mg), administered in combination with ranibizumab was compared to the gold standard monthly ranibizumab injection. Patients receiving the combination of anti-PDGF (1.5 mg) monthly gained a mean of 10.6 letters of vision at 24 weeks, while patients receiving ranibizumab monotherapy gained 6.5 letters ($P = 0.019$). Thus combination treatment resulted in 62 % additional benefit. Moreover, the benefit of the combination treatment was higher at 6 months compared to 3 month of treatment suggesting a benefit of chronic anti-PDGF combination therapy [43]. Further clinical trials are needed in order to study the efficacy of this combination treatment.

Steroids

Triamcinolone acetonide (TA) is one of the first pharmacologic compounds evaluated for the treatment of CNVM secondary to neovascular AMD. Histopathologic study of CNVM in humans and animal models has shown the proliferation both the vascular component, constituted by new blood vessels, and an extravascular component, constituted mainly by inflammatory cells [44].

A short-term retrospective, non-comparative case series study of 30 eyes with neovascular AMD was preformed, treating these eyes with intravitreal injections of bevacizumab (1.25 mg) followed immediately by intravitreal TA (2 mg/0.05 ml) in separate syringes. There was a significant reduction in foveal thickness (164 μm) and subfoveal fluid volume (172 mm^3). Average pre-injection Snellen VA was 0.22 (±0.20), average post-injection VA was 0.32 (±0.25). The need for re-injections, due to recurrence of edema or subfoveal fluid, was reported in 12/30 patients (40 %) with a mean follow-up period of 12.7 weeks [45].

In another small study, sequential intravitreal bevacizumab and TA were administered for the treatment of AMD unresponsive to previous intravitreal bevacizumab injections. This case series included 16 patients who had previously received a mean number of 3.5 (±1.8) injections of bevacizumab without significant improvement in VA and in macular edema. They were then treated with an intravitreal injection of 1.5 mg bevacizumab followed by 20 mg of TA. This treatment resulted in a short-time statistically significant improvement in VA (from 0.8 ± 0.4 to 0.65 ± 0.42 logMAR at 3 months). Vision returned to baseline levels, however, at the 6-month follow-up [46]. In conclusion, a combined treatment of an anti-VEGF drug with triamcinolone may potentially be useful for some patients with exudative AMD if previous anti-VEGF injections have failed. However, to date, there is insufficient evidence of efficacy to recommend its use.

Triple Therapy

Because of the limited effects of anti-angiogenic drugs on stage III, retinal angiomatous proliferation (RAP) lesions, some have advocated the use of triple therapy; involving the use of verteporfin–PDT, an intravitreal anti-VEGF drug, and an intravitreal steroid (dexamethasone or triamcinolone). In a small a prospective open-label study comparing intravitreal ranibizumab with intravitreal ranibizumab combined with PDT with verteporfin and intravitreal TA combined with PDT, 37 eyes of 37 patients with RAP lesions were randomly assigned in one of the three groups. The results of this study showed stabilization of the VA in all three groups. However, there was a significant trend towards a better VA at the end of the follow-up in favor of group 3. Moreover, the

patients in group 3 experienced the greater changes in terms of VA and retinal thickness on OCT among the three groups. In addition no patient in group 3 experienced a worse VA at the end of the follow-up compared with 38.46 % in group 1 and 23.07 % in group 2. In addition, the majority of the patients in group 3 (72.72 %) had better VA at the end compared with 38.46 % in the other two groups. Also, the superiority of group 3 against the other groups is supported by the fact that the average number of injections was statistically significantly lower than that of the other groups. However, a higher rate of complications and RAP recurrences was seen in group 3 [47•].

This treatment option has become popular in Europe and few centers in the USA. The studies supports that the combination of triamcinolone or dexamethasone with an anti-VEGF agent may enhance the anti-inflammatory and -VEGF effects associated with PDT, than either agent alone with PDT. However, the management of RAP remains a challenge and further studies are needed to further determine the effectiveness of these therapies.

Conclusion

To date, anti-VEGF treatment has been shown to be a safe and effective treatment for patients with all subtypes of neovascular AMD. The initial studies, which lead to the FDA approval of this therapy, were based on monthly injection of the agent. These studies all showed that the most significant visual gain occurred in the first 3 months. Subsequent studies designed to evaluated an alternative dosage regimen to the monthly injections, showed that there is only small differences in mean gain in VA emerged between dosing regimens.

Several trials evaluated combination therapies, including PDT, radiation treatment and steroids for wet AMD. Currently, combination therapy is used in patients not responding to monotherapy with anti-VEGF for idiopathic polypoidal choroidal vasculopathy and RAP lesions. Testing of new treatment modalities such as radiation and anti-PEDF are still underway.

Disclosures Miriam Englander: Rishi P. Singh has served as a Consultant for Genentech, Regeneron, Alcon and Bausch and Lomb and has received a grant from Regeneron.

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