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Anti-VEGF in the Treatment of Retinal Disease: A Decade of Clinical Experience

A report from the 2014 Annual Meetings of the American Society of Retina Specialists and American Academy of Ophthalmology

By WAI-CHING LAM, MD, FRCSC and EMMANOUIL MAVRIKAKIS, MD, PhD

Intravitreal anti-vascular endothelial growth factor (VEGF) therapy has been established as a standard of care for exudative retinal diseases including choroidal neovascularization (CNV) secondary to age-related macular degeneration and non-CNV related conditions such as diabetic macular edema and retinal vein occlusion. This issue of *Ophthalmology Scientific Update* highlights several presentations and discussions on safety and efficacy data from pivotal long-term clinical trials of anti-VEGF agents at the annual meetings of the American Society of Retina Specialists (ASRS; August 9-13, 2014; San Diego, California) and American Academy of Ophthalmology (AAO; October 18-21, 2014; Chicago, Illinois) that further expand our clinical knowledge and potential considerations that should be taken into account in daily practice.

Long-Term Outcomes with Anti-Vascular Endothelial Growth Factor (VEGF) Agents in the Treatment of Wet Age-Related Macular Degeneration (AMD)

Recent data on the long-term use of anti-VEGF agents support their benefit in the neovascular ('wet') form of AMD. Researchers also highlighted the potential effects of long-term, frequent use of these agents for retinal diseases related to choroidal neovascularization (CNV), such as loss of response and development of geographic atrophy (GA).

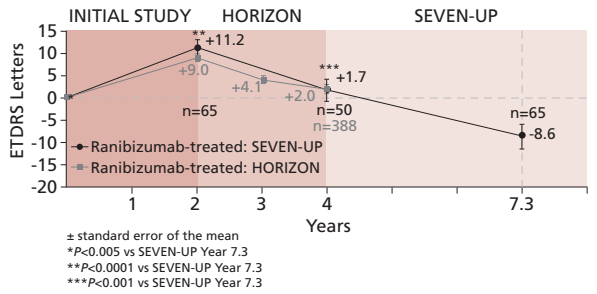
Results were presented from the SEVEN-UP study, which followed 65 ranibizumab-treated participants in the ANCHOR, MARINA, and HORIZON trials for a mean of 7.3 years.[1] Slightly more than one-third (37%) of study eyes achieved the best-corrected visual acuity (BCVA) threshold of 20/70 or better (primary outcome measure); however, the same number worsened to 20/200 or lower. Reduction in BCVA was associated with the presence of subfoveal macular atrophy (MA; $P<0.01$) and an increase in atrophic area ($P<0.0001$). The mean change in Early Treatment Diabetic Retinopathy Study (ETDRS) letter score was -8.6 letters (95% confidence interval [CI] -2.9 to -14.2; $P<0.005$) (Figure 1), although 43% of study eyes had a stable or better letter score from baseline. Bhisitkul et al[2] found that treated eyes experienced one-half the decline in ETDRS letters as fellow eyes (-4.8 versus -9.5 letters) in a cohort of SEVEN-UP participants (Table 1). It is important to note that 35% of the fellow eyes received infrequent treatments outside of these trials with a mean 2.0 injections per eye per year. At year 7, 54% of study eyes were better (≥5 letters) than fellow eyes, compared with 43% at baseline.

To further assess the impact of MA on visual outcomes, a retrospective subanalysis of the HARBOR trial compared visual outcomes in patients with and without baseline atrophy.[3] It was demonstrated that patients with baseline MA (n=123) have similar ETDRS letter gains (+6.7) as those without atrophy (n=904; +9.1) at 24 months. Cysts, atrophy in the fellow eye at baseline, and the absence of subretinal fluid were risk factors for developing atrophy. In addition, monthly anti-VEGF treatment, but not the higher dose (ie, 2.0 mg), was found to be a more significant contributor to the development of atrophy. Of greatest clinical import, all patients who received anti-VEGF therapy experienced improved visual acuity through 2 years, irrespective of any atrophy.

An open-label extension (OLE) of the VIEW 1 trial (N=323)[4] found that patients who received at least quarterly injections of aflibercept (2 mg) lost an average of 3.4 letters between weeks 96 and 208. Patients received a mean of 12.9 injections during a mean of 116.9 weeks (range 4-267 weeks). At week 208, 33% of

Department of Ophthalmology and Vision Sciences, Faculty of Medicine, University of Toronto, 60 Murray St. Suite 1-003 Toronto, ON M5G 1X5

Figure 1: SEVEN-UP Study: Mean change in ETDRS letter score from baseline to mean follow up[1]



ETDRS = Early Treatment Diabetic Retinopathy Study

patients maintained ≥15 letters gain from the VIEW 1 baseline, while 10% lost ≥15 letters. The most common ocular serious adverse events (SAEs) during the extension study were endophthalmitis (0.9%) and retinal hemorrhage (0.6%). The overall incidence of Anti-Platelet Trialists' Collaboration (APTC) defined arterial thromboembolic events (ATEs) was 6.2% and the incidence of intraocular inflammation was 0.34%.

Bressler et al[5] conducted a retrospective cohort study of 75 CNV patients who received anti-VEGF therapy for ≥3.5 years (mean follow-up 4.9 years) to assess the development of GA or predominantly hemorrhagic lesions. At treatment initiation, GA within the boundary of the CNV lesion was present in 4 eyes and outside the boundary in 8 eyes (10%). Although all baseline GA (within or outside a CNV lesion) enlarged over time, no additional eyes developed GA outside the boundary of the CNV lesion. Within 4 years of treatment initiation, however, 5 eyes developed new atrophy within the boundary of the CNV lesion. Although all of these atrophic areas enlarged over time, they remained within the original CNV lesion (atrophic scar). Predominantly hemorrhagic lesions were identified in 6 eyes at baseline, an additional 3 eyes developed hemorrhagic lesions, and new lesions were noted in 1 eye after 3.5 years. Thus, this study suggested that GA typically does not develop outside an area previously occupied by CNV unless such atrophy is present at the time of anti-VEGF treatment initiation. These areas progress over time in a manner similar to what is expected in eyes with GA and without CNV.

Table 1: SEVEN-UP study: mean ETDRS letter scores over time[2]

Time point	Fellow eye	Study eye
Baseline	57.3	53.8
Year 2	58.3	65.8
Year 4	53.6	55.9
Year 7	47.8	49

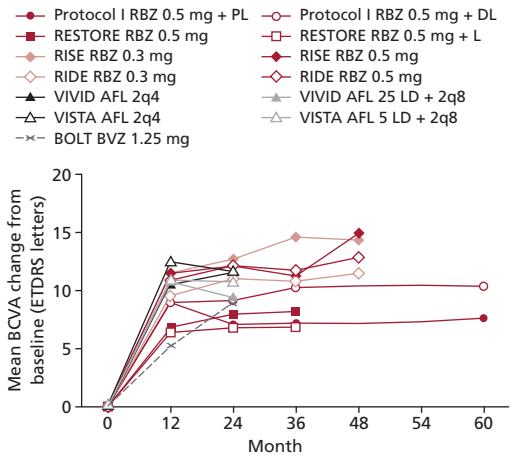
Intravitreal Anti-VEGF for Diabetes-Related Ocular Complications: Clinical Trial Update

Although both diabetic macular edema (DME) and neovascular AMD respond well to anti-VEGF therapy, these are distinct conditions in regard to underlying pathophysiology and natural history. Thus, the frequency and the duration of therapy needed to achieve and maintain the desired visual and anatomical outcomes are different for individuals with DME compared to those presenting with AMD. Furthermore, clinicians treating diabetics have to consider the importance of systemic disease control and lifestyle changes on visual outcomes. Much emphasis has been placed on educating this population about the importance of a healthy lifestyle; however, the results of the Diabetic Retinopathy Clinical Research Network's Protocol M study[6] did not show a benefit of personalized diabetes-related education during regular ophthalmology visits in regard to reduction of hemoglobin A1c levels at 1 year of follow-up. However, when interpreting these data, it is important to take into consideration that the patient's willingness to make appropriate lifestyle changes and adherence to suggested changes are key determinants of successful outcomes. Anecdotal case reports from daily ophthalmology practice clearly demonstrate that patient involvement in the management of their condition and adherence to the treatment plan can have positive outcomes.

A comprehensive overview of anti-VEGF trials in DME by Pieramici[7] highlighted the important efficacy and safety findings to date.

- The greatest visual improvement is observed in the first year of treatment, with a plateau in BCVA gain at 55–65 letters (Figure 2)
- The treatment burden (ie, number of injections required) is markedly reduced after the first year

Figure 2: Reported improvements in best-corrected visual acuity (BCVA) in trials involving anti-vascular endothelial growth factor (VEGF) agents[7]



AFL = aflibercept; BVZ - bevacizumab; RBZ = ranibizumab; DL = deferred laser; L = laser; LD = loading doses; PL = prompt laser.
N's of time points during extension studies are lower than the core studies, outcomes at these times reflect this enrolled subset of patients.

- Greater gains in BCVA are usually achieved in subjects with lower baseline BCVA
- Anti-VEGF agents are superior to laser
- Fixed and PRN dosing result in relatively equal levels of visual improvement, meaning that a PRN treatment strategy is generally as effective as fixed-dose with significantly fewer injections

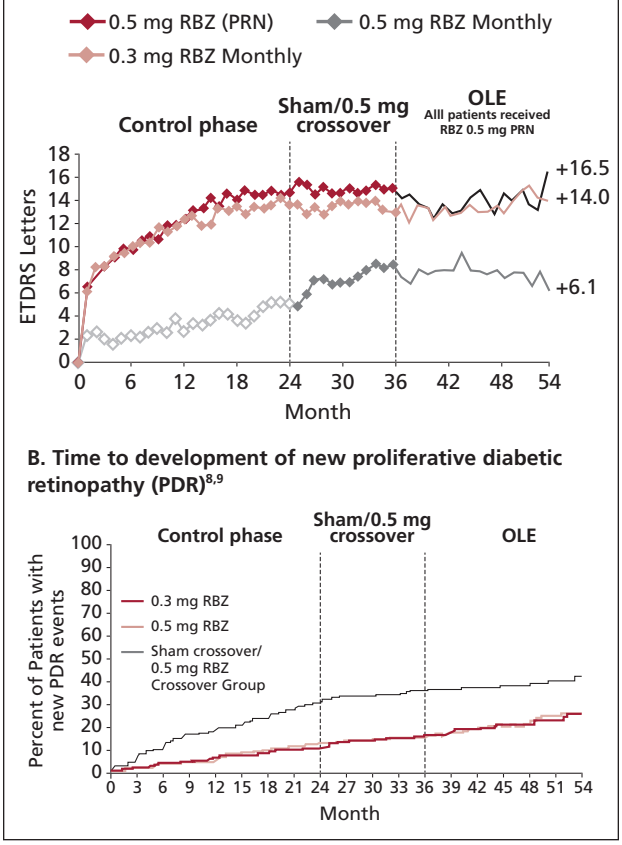
In general, diabetic patients are younger than their AMD counterparts, and for them frequent ongoing intravitreal injections might present a significant burden. The OLE phases of the RISE and RIDE trials provided evidence that the efficacy and safety achieved with initial monthly ranibizumab injections can be maintained with less-than-monthly treatment.[8,9] In the original Phase 3 trials (N=759), monthly injections of ranibizumab (0.3 mg or 0.5 mg) were shown to be significantly superior to sham injection in improving BCVA over 24 months and required significantly fewer macular laser procedures.[10] A crossover of control participants to monthly ranibizumab (0.5 mg) at month 25 revealed higher visual benefit in those receiving ranibizumab from the study outset to month 36, supporting early institution of anti-VEGF therapy.[11]

All patients who completed month 36 of the core studies were eligible to enroll in the OLE,[8,9] according to treatment criteria including evidence as per optical coherence tomography (OCT) of DME and ≥5 ETDRS letter worsening vision at month 36. As needed (PRN) retreatment criteria were designed to maintain the vision gain and the stability of the macular anatomy achieved with monthly injections while adding flexibility to dosing schedules. As shown in Figure 3A, VA gains achieved after 12–36 months of monthly ranibizumab were maintained with the new PRN schedule. Approximately 25% of patients did not require further anti-VEGF therapy based on the PRN treatment criteria, and the mean number of injections over 12 months was 3.8 in patients who required further treatment (mean 4.5 injections/14.1 months of follow-up). The switch from monthly treatment to PRN did not result in loss of vision, recurrence of edema, or progression of diabetic retinopathy. Mean retinal thickness on OCT remained stable and the safety profile of ranibizumab in the OLE appeared similar to that observed in the controlled core studies. Another important finding from the RISE and RIDE trials is that individuals who received early continuous ranibizumab treatment had a lower risk of developing a new proliferative diabetic retinopathy event over time compared with subjects originally randomized to sham (Figure 3B).

A subanalysis of the RISE and RIDE trials assessed patient characteristics associated with treatment frequency during the OLE.[12,13] Compared to patients receiving >7 injections, patients not requiring treatment during OLE had a shorter duration of diabetes, a shorter time from DME diagnosis, better vision, and less edema at baseline (Table 2). This exploratory analysis revealed that early diagnosis and implementation of proper treatment are influential in the attainment of DME remission and maintenance of improvements in vision without the need for continued intravitreal injections.

In terms of effective dosage for DME, the READ 3[14] trial (N=152 eyes) showed that the lower dose of ranibizumab (0.5 mg) demonstrated greater efficacy than the higher dose

Figure 3: RISE and RIDE trials: evidence from the open-label extension (OLE) phase[8]



BCVA = best corrected visual acuity; RBZ = ranibizumab; PRN = as needed

(2 mg). The 6- and 24-month changes in BCVA were +7.0 and +6.8, respectively for the 2 mg group, and were +9.4 and +11.0, respectively, for the 0.5 mg group. The difference at month 24 was statistically superior (*P*=0.02) for 0.5 mg.

Results of the double-masked, randomized, Phase 3 VIVID (N=461) and VISTA (N=402)[15] trials supported the clinical superiority of aflibercept (2 mg every 4 [2q4] or 8 [2q8] weeks fol-

Table 2: RISE and RIDE trials: baseline characteristics associated with more frequent treatment[11,12]

	Injections per year during OLE	
Baseline characteristics	0 injections (n=121)	>7 injections (n=88)
BCVA ETDRS letters, mean (SD)	58.6 (10.9)	54.3 (11.6)
CFT (μm), mean (SD)	440.5 (150.3)	525.5 (160.8)
Duration of CSME (years)	2.1	2.9

SD = standard deviation; CFT = central foveal thickness; CSME = clinically significant macular edema

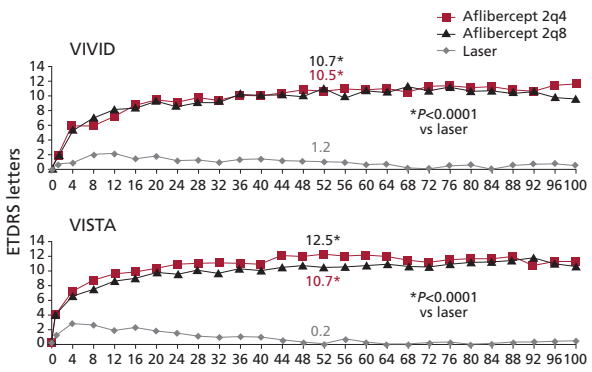
lowing 5 initial monthly doses) compared to laser. Visual benefit was similar between the groups treated every 4 weeks and every 8 weeks (Figure 4). The rates of death and of ATEs were higher in the aflibercept groups than with laser alone. In VISTA, ATEs were experienced by 9 patients in the laser group (5.8%), 11 in the aflibercept 2q8 arm (7.2%), and 13 in the 2q4 arm (8.4%). The equivalent numbers in VIVID were 3 (2.3%), 5 (3.7%), and 8 (5.9%), respectively. Three VISTA patients (1.9%) receiving laser died, and there were 4 (2.6%) and 8 (5.2%) deaths in the 2q8 and 2q4 groups, respectively. In VIVID, there were 1 (0.7%), 6 (4.4%), and 4 (2.9%) deaths in the laser, 2q8, and 2q4 arms, respectively. It must be noted that these studies were not powered to detect a safety difference. A subgroup analysis of the VISTA trial[16] also demonstrated similar efficacy and safety of aflibercept in anti-VEGF naïve patients and those previously treated with an anti-VEGF agent. Over 52 weeks, the changes in BCVA letter score were +10.7, +10.5, and -1.0 (P<0.0001) for 2q4, 2q8, and laser, respectively, among anti-VEGF-experienced patients and +13.8, +10.9, and +1.1 (P<0.0001), respectively, among treatment-naïve individuals.

Anti-VEGF: Safety Update

In his presentation about the risks and benefits of currently used anti-VEGF agents, Rosenfeld emphasized that "the benefits of improved vision from anti-VEGF therapy far outweigh the risks."[17] He pointed to the low incidence of APTC events in the foundation trials such as CATT, IVAN, MARINA, ANCHOR, and VIEW. Despite this evidence, concerns persist regarding the potential for increased systemic and ocular AEs with VEGF inhibition.

A systematic review by Major et al[18] assessed the incidence of AEs (intraocular inflammation, hypertension, and APTC events) in the clinical trials of intravitreal aflibercept for the management of wet AMD, macular edema following central or branch retinal vein occlusion (CRVO and BRVO), and DME. More than 4200 patients in 9 Phase 2/3 clinical trials contributed 5530 patient-years of treatment. They found low incidence rates for these AEs within the different trials and no meaningful differences between events rates for aflibercept and comparators or between fixed and alternative dosing.

Figure 4: VIVID and VISTA trials: mean change in BCVA through week 100[15]



According to a retrospective *post hoc* analysis of 5 DME studies involving ranibizumab for up to 3 years' duration, the relative risk versus control interventions for all ATEs was 0.75 (95% CI, 0.32–1.73) at 12 months.[19] No pattern suggestive of a causal relationship with ranibizumab was evident for cardio- or cerebrovascular events. The relative risks for myocardial and non-myocardial ATEs were 0.70 (0.24–2.07) and 0.98 (0.30–3.19), respectively. At 12 months, 2.4% of patients treated with sham and 1.7% of patients treated with ranibizumab had experienced a myocardial infarction. The rate of nonfatal cerebrovascular accidents was also higher in the control group (6.2%) than among the ranibizumab-treated subjects (1.9%).

A retrospective chart review by Fine et al[20] examined the characteristics, frequency, and management of intraocular inflammation following intravitreal aflibercept injections from November 2011 through June 2013. There were 28 cases of intraocular inflammation following 5905 aflibercept injections in 1660 patients, which translates to an infection rate of 0.47%. The majority of patients returned to baseline VA within 1 month with the application of topical corticosteroids. Higher rates of ocular inflammation with aflibercept compared to ranibizumab were reported by the PLANET study, an open-label, evaluator masked clinical trial conducted at a single centre.[21] One of 35 (2.9%) ranibizumab-treated and 10 of 53 (18.9%) aflibercept-treated patients had mild anterior chamber inflammation – defined as any cell or flare in the anterior chamber, graded according to the Standardization of Uveitis Nomenclature working group classifications – at Visit 1 (P=0.04).

Lessons From Real-World Experience

In order to understand treatment patterns of anti-VEGF use for neovascular AMD and DME in real-world clinical practice, Kiss et al[22] conducted a retrospective cohort study of claims data in the United States (US) for aflibercept (2.0 mg) or ranibizumab (0.5 mg) to treat AMD and for ranibizumab (0.3 mg) for DME. Multivariable regression determined that neither number nor costs of injections differed significantly between aflibercept and ranibizumab at 6- or 12-month follow-up. Injections for AMD were 3.7±1.4 for aflibercept and 3.7±1.7 for ranibizumab at 6 months and 5.0±2.7 versus 5.0±3.1, respectively, at 12 months. The mean number of injections for DME patients treated with ranibizumab was 3.0 at 6 months and 4.3 at 12 months. Mean costs over 6 months were $7277 (ranibizumab for AMD), $6757 (aflibercept for AMD), and $3655 (ranibizumab for DME), and the equivalent 12 month costs were $9894, $10 288, and $5217, respectively. These initial results point to fewer injections being administered to DME patients compared with those who have AMD.

Claims and registry data have shown lower use of anti-VEGF agents in clinical practice compared with trials. To examine the impact of this on vision outcomes in DME, Holekamp et al[23] conducted an analysis of data from the electronic medical records of a large US health system. At 12 months, the mean number of anti-VEGF injections was 2.6. Mean corrected VA change from baseline was +4.0 letters at 6 months and +3.7 letters at 12 months using last observation carried forward. At 12 months, 18.1% and 13.8% of patients gained 2 and 3 lines, respectively,

while 11.7% and 8.5% lost 2 and 3 lines, respectively. Thus, this study confirms that less frequent anti-VEGF injections result in lower VA gain compared with landmark trials.

LUMINOUS is a prospective, 5 year, global, observational, multicentre study with the objective to evaluate the long-term safety, effectiveness, and treatment patterns of intravitreal ranibizumab 0.5 mg in routine clinical practice across all approved indications.[24] The goal is to enroll 30 000 patients by March 2015. As of September 1, 2014, enrollment was at 26 664 patients from 40 countries, including 81.5% with wet AMD, 12.0% with DME, 3.2% with BRVO, 2.6% with CRVO, and 0.7% with myopic CNV. Age range, ethnic diversity, and presence of comorbidities were wider than that of pivotal trials. One-year follow-up data available for 9790 patients recruited prior to March 2013 indicated that treatment-naïve patients gained vision from baseline (mean letter change: wet AMD, +4.4; DME, +4.5; BRVO, +7.0; CRVO, +13.2). Patients who were already on ranibizumab at the time of enrollment into the study either gained or maintained vision (mean letter change: wet AMD, -1.5; DME, +3.2; BRVO, +8.0; CRVO, +1.4), with relatively low numbers of injections and monitoring visits. Myocardial infarction, pneumonia, and cerebrovascular incidents were the most frequent non-ocular SAEs, occurring in about 0.4% of patients. The most frequent ocular SAEs were endophthalmitis and retinal detachment reported in 0.1% of treated patients.

Individualized Versus Fixed Treatment Schedule – The Dilemma Continues

Beyond the choice of individual anti-VEGF agent, the determination of best treatment schedule for the individual patient has also been a longstanding point of debate.

According to a retrospective chart review by Peden et al[25] of 109 patients with wet AMD, long-term (≥5 years) continuous fixed dosing anti-VEGF therapy (every 4-8 weeks; average of 10.5 injections per year) is effective in preserving vision. They found that the peak letter gain (16.1 letters) was achieved at 2 years, and that VA declined slowly (average of -0.54 letters per year) over the next 5 years. After 5 and 7 years of treatment, 46.8% and 43.2% of patients, respectively, maintained driving vision.

Several presentations, however, supported the benefit of treat-and-extend regimens. In a study by Regillo et al,[26] 196 patients (212 eyes) who had initially received monthly ranibizumab or bevacizumab for ≥1 year until there were no signs of CNV activity were then extended by intervals of 1-2 weeks as long as no CNV activity was noted on examination. Mean VA improved from 20/139 at baseline to 20/79 after 1 year of treatment (P<0.001) and remained stable at both 2 years (20/69; P<0.001) and 3 years of follow-up (20/65; P<0.001). Mean central retinal thickness decreased from 351 µm at baseline to 285 µm following 1 year of treatment (P<0.001) and remained stable at 2 and 3 years of follow-up (275 µm and 276 µm, respectively; P<0.001 for both). Thus, the treat-and-extend anti-VEGF treatment regimen is effective in achieving and maintaining visual and anatomical improvements in patients with wet AMD for up to 3 years. A systematic review of wet AMD studies by Yee et al[27] demonstrated better visual outcome with a treat-and-extend regimen (7 studies) over PRN treatment (85 studies). At 1 year, the treat-and-extend group experienced a greater mean improvement in VA than the PRN group (+9.8 versus +5.4 ETDRS letters), albeit with more injections (7.6 versus 5.6). The authors cautioned that randomized clinical trials are warranted to confirm these findings. Eichenbaum presented 6 month data from their 2 year open-label, randomized study (N=20) comparing monthly and treat-and-extend ranibizumab (0.3 mg for each arm) in patients with DME.[28] Patients in the treat-and-extend group received monthly injections until a dry or stable macula was achieved, then their treatment was extended by 2-week increments to a maximum of 8 weeks. The investigators identified a trend toward higher VA gain in the treat-and-extend group than the monthly group (+12.6 versus +10.7 letters) and better OCT improvement with an average of 1 fewer injection.

Houston et al[29] found that the treat-and-extend approach is affected by the vitreo-macular interface. Patients with vitreomacular adhesions (VMAs; n=153 eyes) required more injections at 1 year (8.4 versus 7.4; P=0.001) and 2 years (6.7 versus 5.5; P=0.027) compared with non-VMA subjects (n=51 eyes). One and 2 year gains in VA (≥3 lines) were similar in the 2 groups. The mean longest extension between injections was 10.1 weeks for VMA patients compared to 11.8 weeks in non-VMA subjects.

Emerging Evidence for RVO and Myopic CNV

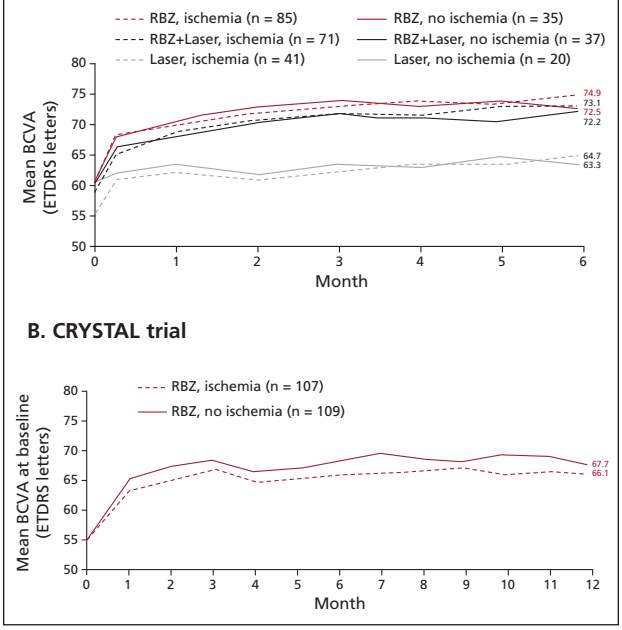
RVO – From Initial Workup to Treatment Considerations

As underlined by Hayreh as part of Retina 2014 preceding AAO 2014, anti-VEGF agents are effective in reducing macular edema but do not cure the disease. Furthermore, after 4 years of retreatment with anti-VEGF, only 44% of CRVO patients experienced resolution of their edema (defined as no intraretinal fluid for ≥6 months after the last injection).[30] Thus, additional research in this therapeutic area is needed.

The efficacy and safety of ranibizumab in RVO has been established in 2 12 month, Phase 3 trials (CRUISE and BRAVO) and in extension trials up to 4 years.[30-35] BRIGHTER (BRVO) and CRYSTAL (CRVO) are ongoing 24 month trials designed to assess long-term efficacy and safety of flexible, stabilization criteria-driven, PRN dosing of ranibizumab 0.5 mg in a broad population of RVO patients.[36] In both the CRYSTAL and BRIGHTER trials ranibizumab with or without laser was superior to laser alone, and provided similar BCVA gains for ischemic and non-ischemic patients (Figures 5A,B). It was also determined that ranibizumab treatment was particularly effective in patients with lower baseline BCVA and shorter disease duration.

The Phase 4 SHORE trial[37] found no significant difference in BCVA gain over 15 months of PRN (21.0 letters) versus monthly (18.7 letters) ranibizumab treatment (0.5 mg) for macular edema secondary to BRVO or CRVO. A sub-analysis of this trial[38] evaluated the impact of intraretinal edema on BCVA gains in patients with RVO randomized to the 2 dosing regimens. The investigators determined that the mean gain in BCVA among patients with edema was 9.6 letters lower at 7 months and 9.3 lower at 15 months than subjects without edema (P<0.001 at both time points). The presence of edema was also associated with a lower rate of gaining ≥15 letters and of achieving 20/40 vision.

Figure 5: BRIGHTER and CRYSTAL trials: vision gains in the presence and absence of ischemia[36]



In the double-masked, Phase 3 VIBRANT trial,[39] 183 treatment-naïve patients with unilateral macular edema secondary to BRVO were randomized to receive either intravitreal aflibercept 2 mg every 4 weeks or grid laser from baseline to week 20.[38] From week 24 onward, patients in the aflibercept group received aflibercept 2 mg every 8 weeks, and if necessary rescue laser at week 36. Patients in the laser group who required rescue treatment could receive aflibercept 2 mg every 8 weeks after 3 initial monthly doses. The proportion of patients who gained ≥15 letters from baseline to week 24 (primary endpoint) was 52.7% in the aflibercept and 26.7% in the laser group (P<0.001).[38,39] At week 52, the proportions of patients who gained ≥15 letters were 57.1% of patients treated with aflibercept and 41.1% of patients treated with laser. The BCVA gain was 17 letters at 24 weeks and 17.1 at week 52 when switched to q8w dosing. About one-third of patients had a decrease in retinal nonperfusion. The most common ocular AEs in patients treated with aflibercept were conjunctival hemorrhage (19.8%) and eye pain (4.4%). Traumatic cataract was the only ocular SAE, occurring in one patient treated with aflibercept. The incidence rates of non-ocular SAEs were 8.8% and 9.8% in the aflibercept and laser groups, respectively.

Myopic CNV

CNV secondary to pathologic myopia (or myopic CNV) is a common cause of vision impairment in patients younger than 50 years. Recent evidence demonstrated the benefit of anti-VEGF therapy over photodynamic therapy (PDT) in the treatment of myopic CNV.

The recently published REPAIR[41] (N=65) and RADIANCE[42] (N=277) trials demonstrated mean gains from baseline in BCVA scores of 13.8 to 14.4 letters over 12 months with intravitreal ranibizumab. The gain with verteporfin PDT in RADIANCE (vPDT given on day 1, and treatment with ranibizumab or vPDT at investigators' discretion from month 3) was 9.3 letters. There were no reports of deaths or cases of endophthalmitis or MI in RADIANCE.

In the MYRROR trial,[43] 122 patients with myopic CNV were randomized to intravitreal aflibercept or sham in a 3:1 ratio. Patients assigned to the aflibercept group received a single 2 mg injection at baseline followed by additional aflibercept injections according to predefined retreatment criteria (in case of CNV persistence/recurrence) or sham injection every 4 weeks until week 44. Patients in the sham group received sham injections through week 20, a single 2 mg injection of intravitreal aflibercept at week 24, followed by additional injections (aflibercept or sham) according to assessment of the same predefined retreatment criteria every 4 weeks through week 44. At week 24 (primary endpoint), the mean changes in BCVA were +12.1 letters among patients in the aflibercept group and -2 letters in the sham group (P<0.0001). The incidence of SAEs was 7.7% in the aflibercept group and 3.2% in the sham group.

Beyond the Current Use of Intravitreal Anti-VEGF Therapies

Although the data overwhelmingly support the effectiveness of anti-VEGF agents in the management of retinal diseases, the frequency (often monthly) of intravitreal injections presents a significant burden to patients, caregivers, treating clinicians and their staff, as well as the healthcare system. This factor is likely a significant contributor to the magnitude of anti-VEGF undertreatment.[23,44] In a 2006–2010 analysis of about 500 000 Medicare beneficiaries, rates of anti-VEGF discontinuation were 57% within the first year and 71% within the first 2 years.[44] Thus, a significant amount of research is geared toward finding innovative solutions that will reduce injection burden (more effective delivery, longer duration of effectiveness) while providing the best possible visual outcomes.

Presenters outlined the research to date on promising innovative approaches for AMD, including gene therapy[45] and encapsulated cell technology (ECT).[46] Gene therapy is a treatment in which genetic material is introduced in cells, either to compensate for structurally abnormal or missing genes or to make beneficial proteins. Gene therapy in development for wet AMD includes a VEGF-binding protein that consists of domain 2 of Flt-1 (isoform of the VEGF receptor 1) linked to a human immunoglobulin G_1 heavy chain Fc fragment (sFlt01). This was combined with an adeno-associated virus (AAV) to produce AAV2-sFlt01. AAV2-sFLT-01 is designed to stimulate retinal cells to continuously produce the antagonist to VEGF, thereby halting the production of the abnormal and leaky blood vessels that leads to progressive vision loss. Two modes of AAV2-sFlt01 delivery to the eye are under investigation – intravitreal and subretinal.

The ECT platform utilizes a genetically engineered retinal pigment epithelial cell line that constitutively produce therapeutic proteins.[46] These are contained within a device that is surgically implanted into the vitreous cavity through a ≤3 mm scleral incision. ECT product candidate, NT-503, has been engineered

Table 3: Change in severity of fibrosis with anti-PDGF / anti-VEGF combination versus ranibizumab monotherapy[48]

	Severity of fibrosis (sum of absolute grades)			Severity of fibrosis (mean value - grades)				Progression of fibrosis	
Group	Baseline	Week 24	Difference	Baseline	Week 24	Difference	Development of fibrosis[a]	Number of patients	% developing fibrosis
Combination therapy (n=33)	21	53	32	0.63	1.6	0.97	0.1	9	0.27
Monotherapy (n=37)	10	84	74	0.27	2.27	2	0.51	20	0.54

[a] % without any fibrosis at baseline developing fibrosis at week 24; [b] % with 2-step increase in fibrosis from baseline to week 24

to continuously produce a soluble VEGF receptor fusion protein for the treatment of wet AMD. This product is undergoing dose-escalation studies.

It has also been observed that prolonged anti-VEGF treatment may lead to resistance. One of the proposed mechanisms of resistance to anti-VEGF agents involves stimulation of pericytes with platelet-derived growth factor (PDGF) to form a protective anti-VEGF barrier around the neovascular complex.[47] Conversely, blocking PDGF leads to pericyte stripping, which in turn increases sensitivity of endothelial cells to anti-VEGF. In addition, PDGF may be associated with the development of fibrosis, which contributes to vision loss in AMD. These findings led to investigations of combining anti-PDGF with anti-VEGF in the treatment of wet AMD. The results of a Phase 2b trial (N=449 patients) that assessed the safety and efficacy of a PDGF inhibitor (0.5 mg and 1.5 mg) in combination with ranibizumab (0.5 mg) compared to ranibizumab monotherapy demonstrated the superiority of the 1.5 mg combination therapy over ranibizumab monotherapy at 24 weeks (+10.6 versus +6.5 letters; *P*=0.019).[48] A subanalysis of the study by Chakravarthy et al[49] assessed the severity of fibrosis (graded on a 0–4 categorical scale) in eyes treated with combination therapy (n=33) versus ranibizumab monotherapy (n=37). At week 24, 27% of eyes receiving combination therapy and 54% treated with ranibizumab monotherapy experienced a ≥2 step worsening of fibrosis. Fibrosis developed in more than half (51%) of monotherapy and 10% of combination therapy eyes that had no fibrosis at baseline (Table 3).

Conclusion

These recent annual meetings of the ASRS and AAO provided more extensive evidence that the long-term benefits of anti-VEGF therapy outweigh potential risks in the prevention of vision loss secondary to CNV and non-CNV related retinal conditions. The findings presented at these meetings reflect the steady progress in improving the selection of appropriate agent and treatment schedule to maximize effectiveness and safety. The growing body of real-world studies underlines the results of clinical trials while at the same time highlighting the underuse of anti-VEGF agents. New treatment delivery methods involving genomics and ECT offer promise toward more efficient and less disruptive management.

Dr. Lam *is a Professor, Vice-Chair of Education, and Director of Continuing Professional Development, Department of Ophthalmology & Vision Sciences, University of Toronto, and University Health Network – Toronto Western Hospital, Toronto, Ontario.* ***Dr. Mavrikakis*** *is a Consultant Vitreoretinal Surgeon, Ophthalmology Department, General Hospital of Athens "G. Gennimatas", Athens, Greece.*

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