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Management of Retinal Disease in the Era of Anti-VEGF Therapies

A report from the 31st Annual Meeting of the American Society of Retina Specialists (ASRS)

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Reported and discussed by
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Nearly a decade has passed since the introduction of anti-vascular endothelial growth factor (VEGF) therapy to the retinal disease treatment armamentarium. Since then, anti-VEGF agents have fast become a mainstay in the management of conditions such as age-related macular degeneration, retinal vein occlusions, diabetic retinopathy, and diabetic macular edema. As the initial excitement in the novelty of new vision-saving treatments diminishes and clinicians become increasingly experienced in using these agents, numerous practical questions start to emerge, including optimization of dosing and treatment schedules, dealing with sub-optimal responders, ocular and systemic safety, treatment duration, and long-term efficacy outcomes. This issue of *Ophthalmology Scientific Update* provides a summary of presentations from the 31st Annual Meeting of the American Society of Retina Specialists that addressed these issues, and will be reviewed in the context of Canadian ophthalmology practice for clinicians treating patients with retinal disease.

Update on Pharmacological and Pharmacokinetic Aspects of Anti-VEGF Therapies and Their Clinical Relevance

The 3 anti-vascular endothelial growth factor (VEGF) agents currently used to treat various retinal conditions display significant differences in their molecular structure, weight, and affinity for VEGF. Bevacizumab is a full-length recombinant humanized monoclonal antibody that is approved by Health Canada for systemic use in oncology, but not for ocular administration.[1] Ranibizumab is a humanized recombinant monoclonal antibody fragment designed specifically for intravitreal use.[2,3] Aflibercept is an anti-VEGF recombinant fusion protein that, in addition to VEGF, also targets placental growth factor (PlGF).[4] Thus, there is an ongoing dilemma whether and to what degree their structural differences affect the pharmacokinetics of these agents, particularly the transport from the eye into the systemic circulation. A more important question is the impact of these agents on systemic VEGF levels and whether this correlates with the risk of systemic adverse events. The IVAN trial, which compared ranibizumab with bevacizumab in Europe, for example, found significantly lower serum VEGF levels after treatment with bevacizumab compared to ranibizumab.[5]

To provide more information regarding the systemic exposure of intravitreally administered anti-VEGF therapies, Robert Avery, MD, presented data comparing the serum drug and plasma VEGF levels in 90 treatment-naïve patients with neovascular age-related macular degeneration (AMD; n=45) and retinal vein occlusion (RVO; n=45) following intravitreal administration of ranibizumab, bevacizumab, and aflibercept.[6] Systemic exposure was highest with bevacizumab, followed by aflibercept, then ranibizumab (Figure 1). The pattern of exposure was similar in AMD and RVO patients. Dr. Avery speculated that this is due to the Fc binding associated with both aflibercept and bevacizumab. After 1 dose aflibercept appears to reduce plasma VEGF the most, and after 3 doses both aflibercept and bevacizumab display a substantial reduction of plasma VEGF for 30 days post-injection. The effect of intravitreally administered anti-VEGF on systemic adverse events continues to be a source of scientific speculation as large clinical trials with these agents were not powered to assess safety. To that end, Dr. Avery reminded the audience of a recent meta-analysis that included 4 trials (IVAN, CATT, MANTA, and GEFAL), presented at the 2013 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO) 2013

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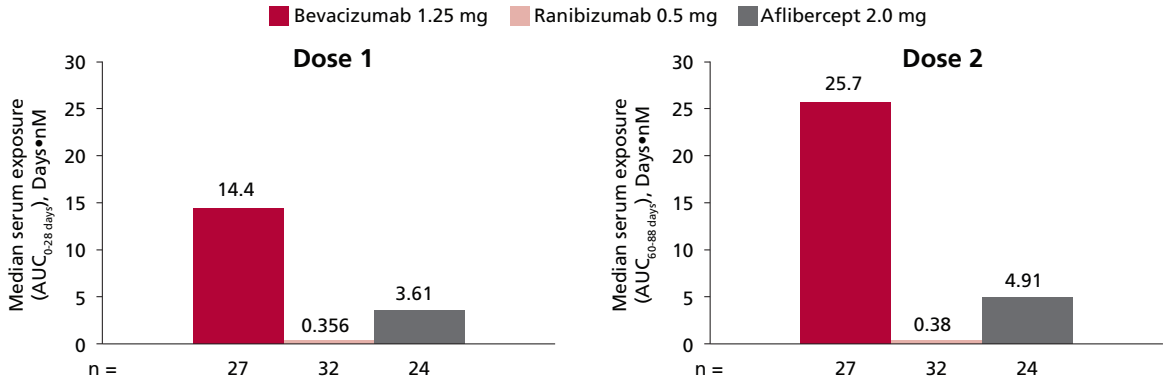
Figure 1: Comparison of systemic pharmacokinetics post-anti-VEGF intravitreal injections of ranibizumab, bevacizumab, and aflibercept[6]



Geometric Mean Ratios	
AFB/RBZ (90% CI)	9.68 (7.92-11.8)
BEV/RBZ (90% CI)	38.3 (32.9-44.6)

Geometric Mean Ratios	
AFB/RBZ (90% CI)	13.1 (11.1-15.4)
BEV/RBZ (90% CI)	70.4 (60.1-82.3)

VEGF = vascular endothelial growth factor; AFB = aflibercept; RBZ = ranibizumab; BEV = bevacizumab; AUC = area under the curve; CI = confidence interval

by Laurent Kodjikian, MD, PhD.[7] Despite the fact that these trials were conducted at different times and in different countries, they all show a similar relative risk of about 1.34 for systemic adverse events with bevacizumab compared to ranibizumab (Figure 2).

Data presented by Gerhard Kieselbach, MD, confirmed that VEGF plasma levels decrease significantly over the 4-week period following a single injection of bevacizumab in patients with AMD and diabetic macular edema (DME).[8] Median VEGF plasma levels of patients with AMD and DME before bevacizumab were 89.7 pg/mL and 72.2 pg/mL, respectively. Significant decreases were noted in the AMD (25.1 pg/mL) and DME (13.7 pg/mL) groups 1 week post-injection. After one month the levels were 22.8 pg/mL in AMD and 17.1 pg/mL in DME patients.

These data add to the evidence that molecular structure plays a role in systemic exposure of intravitreally administered anti-VEGF therapies. However, the clinical relevance remains unknown.

Figure 2: 1-year safety meta-analysis comparing bevacizumab and ranibizumab[7]

Serious systemic adverse event

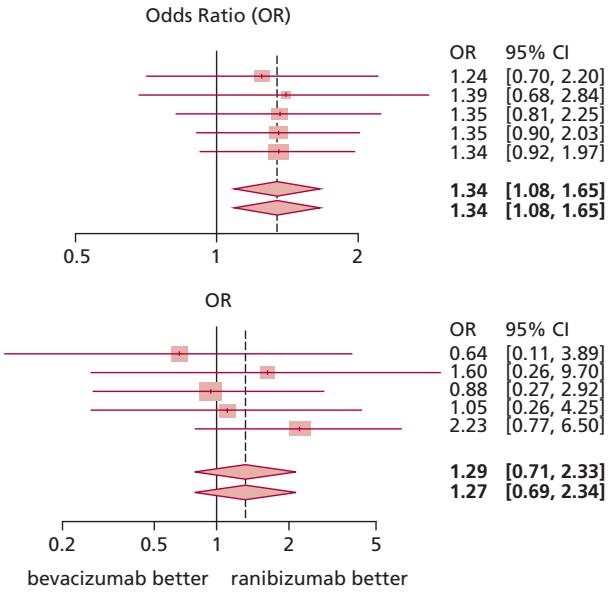
Study	Bevacizumab Events	Bevacizumab Total	Ranibizumab Events	Ranibizumab Total	OR	95% CI
GEFAL	30	246	24	239	1.24	[0.70, 2.20]
MANTA	19	154	15	163	1.39	[0.68, 2.84]
IVAN (treat, comparison)	37	296	30	314	1.35	[0.81, 2.25]
CATT (monthly)	64	286	53	301	1.35	[0.90, 2.03]
CATT (as needed)	77	300	61	298	1.34	[0.92, 1.97]
Fixed effect model		**1282**		**1315**	**1.34**	**[1.08, 1.65]**
Random effects model					**1.34**	**[1.08, 1.65]**

Heterogeneity: I-squared=0%, tau-squared=0, P=0.9993

Deaths

Study	Bevacizumab Events	Bevacizumab Total	Ranibizumab Events	Ranibizumab Total	OR	95% CI
GEFAL	2	246	3	239	0.64	[0.11, 3.89]
MANTA	3	154	2	163	1.60	[0.26, 9.70]
IVAN (treat, comparison)	5	296	6	314	0.88	[0.27, 2.92]
CATT (monthly)	4	286	4	301	1.05	[0.26, 4.25]
CATT (as needed)	11	300	5	298	2.23	[0.77, 6.50]
Fixed effect model		**1282**		**1315**	**1.29**	**[0.71, 2.33]**
Random effects model					**1.27**	**[0.69, 2.34]**

Heterogeneity: I-squared=0%, tau-squared=0, P=0.7173



Local effects of anti-VEGF therapies were also reviewed. To understand the potential local inflammatory effects following injection of different anti-VEGF agents, Nneka Brooks, MD, and colleagues compared the change in anterior-chamber flare.[9] There was a statistically, but not clinically, significant increase in flare following bevacizumab injection (n=26 eyes) compared to ranibizumab (n=21 eyes), but no statistically significant difference in change in flare between aflibercept (n=14 eyes) and the other 2 agents.

Sophie Bakri, MD, discussed the penetration and transportation of intravitreal bevacizumab and ranibizumab into the optic nerve of the fellow eye.[10] She reported that her group detected intravitreal bevacizumab and ranibizumab in the optic nerves of both the injected and fellow eye of 6 Dutch belted rabbits at 1 month post-intravitreal injection. This contrasts with her group's previous published results,[11] which found no fellow eye penetration of intravitreal ranibizumab at any time point over the 29-day study period. They also determined in this rabbit model a significantly shorter vitreous half-life of 0.5-mg ranibizumab (2.88 days) than that of 1.25-mg bevacizumab (4.32 days). These new results imply that there may be specific mechanisms that transport intravitreal drugs via the optic nerve to the fellow eye. Further investigation regarding drug transportation and localization after intravitreal drug delivery will contribute to the understanding of some of the long-term effects of anti-VEGF therapies.

Management of Wet AMD with Anti-VEGF Therapy: Focus on Individual Treatment

Lessons from the HARBOR trial – prn 0.5 mg ranibizumab sufficient for most patients

Several presentations at the ASRS 2013 meeting discussed the clinical relevance of the latest evidence from the Phase III, 24-month, randomized, multicentre, double-masked, dose-response HARBOR trial.[12] The trial randomized 1097 untreated patients with subfoveal wet AMD to intravitreal ranibizumab injections (either 2.0 mg or 0.5 mg) dosed monthly or as needed (prn) after 3 monthly loading doses. According to Brandon Busbee, MD, primary investigator of HARBOR, significant and clinically meaningful increases in best-corrected visual acuity (BCVA) observed in all 4 treatment groups at 12 months (primary endpoint) were maintained at 24 months (Table 1).[13] In the second year of treatment, the 0.5 mg prn group received an average of 5.6 injections, with 93% of these individuals not requiring monthly dosing, and the mean treatment interval for this group was 9.9 weeks after 3 monthly loading doses. This indicates that an individualized treatment approach with ranibizumab 0.5 mg prn may be appropriate for most patients with wet AMD. In regard to safety outcomes, there was no evidence that dose response or dose exposure was related to key ocular or nonocular adverse events. After 24 months, the ocular and systemic safety profile of ranibizumab was similar to that reported by previous trials and was consistent across all treatment groups. Serious ocular adverse events were rare.

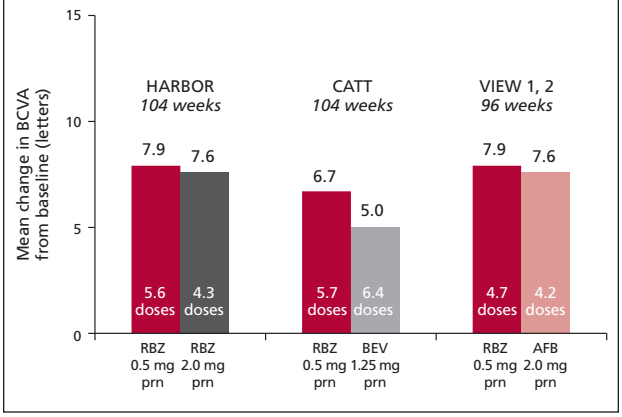
Table 1: HARBOR trial: gains in best-corrected visual acuity (BCVA) over 2 years[13]

Group	Change in letters	Patients who gained ≥15 letters	Average number of injections	Letter change from month 12 to 24
Ranibizumab 0.5 mg monthly	+9.1	34.5%	21.4	-1.0
Ranibizumab 2.0 mg monthly	+8.0	37.6%	21.6	-1.2
Ranibizumab 0.5 mg prn	+7.9	33.1%	13.3	-0.3
Ranibizumab 2.0 mg prn	+7.6	34.8%	11.2	-1.0

To put these data in perspective, Dr. Busbee compared the mean changes in BCVA from baseline for patients who received less than monthly dosing in year 2 of the HARBOR, CATT[14] and VIEW[15,16] trials (Figure 3). He pointed out that, despite baseline differences between these trials (ie, trials were conducted at different time points and included different patient populations and criteria), there were similarities in visual outcomes and injection frequency.

Neil Bressler, MD, presented patient-reported visual function outcomes measured by the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25).[17] The questionnaire was administered at baseline and at months 12 and 24 to groups of individuals receiving ranibizumab 0.5 mg monthly (n=275) or prn (n=275) and ranibizumab 2.0 mg monthly (n=274) or prn (n=273).[18] Baseline mean NEI VFQ-25 varied from 75.2 to 77.2, indicating poor visual function. After 2 years of treatment, mean composite scores increased in the 4 groups by 4.8, 2.6, 3.6, and 2.7 points, respectively. Significant improvements (≥10 points) in the composite, near, distance, and visual specific dependency were observed in 20%–30% of individuals across all 4 groups. Thus, as concluded by Dr. Bressler, patient perception of vision-related function paralleled results for visual acuity in all dosing

Figure 3: Less than monthly dosing: HARBOR, CATT, and VIEW Year 2[13]



Clinical dose and regimen of ranibizumab and aflibercept, but not bevacizumab, showed similar clinical outcomes

prn = as needed

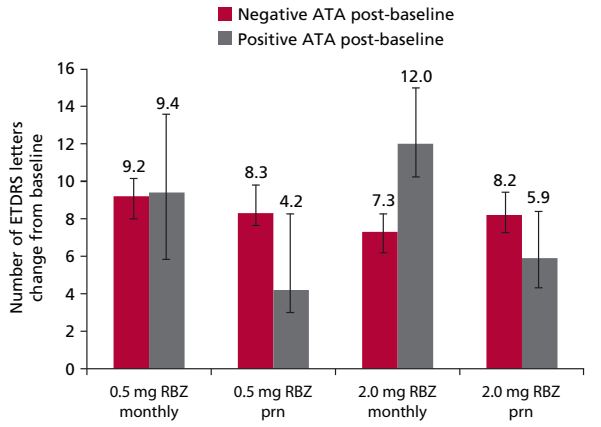
groups. These data are in accordance with a recent article by Mitchell et al[19] demonstrating benefits in patient-reported visual function outcomes with ranibizumab in individuals with DME.

Another subanalysis of the HARBOR trial was presented by Karl Csaky, MD, PhD, whose group assessed the relationship between the presence of antitherapeutic antibodies (ATAs) and the response to treatment.[20] The percentages of ATA-positive patients at months 12 and 24 were 6%–8% for ranibizumab 0.5 mg and 9%–12% for ranibizumab 2.0 mg, with a slightly higher rate in the monthly vs. prn groups. However, the appearance of ATAs had no effect on VA at month 24, and there was no noticeable difference in mean VA between antibody-negative and antibody-positive patients (Figure 4). The presence of ATAs did not affect drug pharmacokinetics or the percentage of patients who gained ≥3 lines of letters at 24 months. Dr. Csaky concluded that the development of ATAs in ranibizumab-treated patients does not appear to affect pharmacokinetic, visual, or anatomic treatment responses and as such cannot be used as an explanation for the loss of response to ranibizumab observed in some patients. This suggests that other factors may be involved.

Similar to the ANCHOR[21] and MARINA[22] trials, HARBOR data also demonstrated that ranibizumab treatment leads to a consistent regression from baseline in classic choroidal neovascular (CNV) area and total CNV area, as presented by John Kitchens, MD.[23] Furthermore, in the HARBOR trial the classic CNV component was the most sensitive to ranibizumab treatment: almost all patients experienced 100% regression after 12 months of treatment. Ranibizumab also reduced CNV thickness on spectral domain optical coherence tomography (SD-OCT) and led to regression of total CNV area from baseline as seen on fluorescein angiography (FA).

In summary, the HARBOR trial suggested that a regimented dosing schedule is unnecessary when treating wet AMD patients with ranibizumab. While some individuals with wet AMD require very little treatment to improve VA, others are optimally managed with more frequent treatment. An individualized treatment approach provides good visual outcomes while decreasing injection burden. Until the characteristics of patients who require frequent injections are better defined, careful follow-up and monitoring are necessary to ensure that anti-VEGF activity is kept to a minimum to keep the disease under control.

Figure 4: HARBOR trial: no apparent effect of antitherapeutic antibody (ATA) status on BCVA at month 24[20]



ATA status did not appear to affect in a consistent manner the number of Early Treatment Diabetic Retinopathy Study (ETDRS) letters gained from baseline across dosing regiments, given the large variability in results.

Lessons from the VIEW trials – effect of retinal fluid on vision outcomes

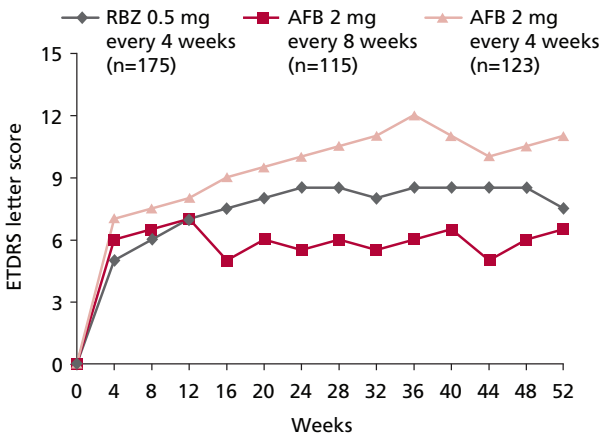
The VIEW trials[15,16] were 2 similarly designed Phase III studies of neovascular AMD that compared monthly and every 2 month dosing of intravitreal aflibercept with monthly ranibizumab. VIEW 1 was conducted in North America, and VIEW 2 was performed in Europe, Asia, and Latin America. In both trials, patients were randomized to 0.5 mg aflibercept every 4 weeks (0.5q4), 2 mg aflibercept every 4 weeks (2q4), 2 mg aflibercept every 8 weeks (2q8) after 3 initial monthly injections, or ranibizumab 0.5 mg every 4 weeks (Rq4) during the first year of treatment. During the second year, patients were evaluated monthly to determine the need for treatment and were treated at least every 12 weeks.

The mean gain in BCVA at week 52 (primary endpoint) was similar among the 4 treatment arms, ranging from 8.3 letters in 0.5q4 to 9.3 in 2q4 group.[15] During the second year there were modest decreases of BCVA in all 4 treatment groups, ranging from 0.8 letters in Rq4 to 1.7 in the 2q4 group.[16] The proportion of patients who maintained a gain of ≥3 lines of BCVA at 96 weeks was in the range of 30%-33%.

Two subanalyses of the VIEW trials assessed the effect of early persistent retinal fluid on subsequent visual and anatomical outcomes. Persistent fluid was defined as fluid on all study visits through week 12 (measured at baseline, weeks 4, 8, and 12). The analysis presented by Glenn Jaffe, MD, included 1759 patients with known fluid status after 3 monthly injections in the Rq4, 2q4, and 2q8 groups from the VIEW studies.[24] At week 12, 29.4%, 18.8% and 20.3% of patients in the Rq4, 2q4, and 2q8 groups, respectively, presented with persistent retinal fluid (relative risk of ranibizumab versus aflibercept 1.51 [1.27,1.78]). The VA improvement for the 2q4 group from week 12 to week 52 (Figure 5) was consistently greater than in the 2q8 and Rq4 groups (P=0.002 and P=0.033, respectively); mean VA change over this time frame in the 2q8 and Rq4 groups did not differ (P=0.19). Similar patterns were seen for the proportion of patients gaining 5, 10, or 15 letters or those losing 5 or 10 letters. Changes in VA did not differ between treatment groups in eyes without persistent retinal fluid. Based on these data, the investigators concluded that patients with early persistent fluid treated with aflibercept every 8 weeks may have had additional improvement in VA outcomes if they had been given subsequent monthly injections. This further emphasizes the need for individualized treatment of patients with wet AMD and points out that an 8-week treatment schedule may not be an optimal approach for all patients treated with aflibercept.

The second subanalysis of the VIEW trials, presented by Seenu Hariprasad, MD, discussed the association between

Figure 5: VIEW trials: mean change in BCVA at week 52 in patients with persistent fluid* [24]



* Persistent fluid was defined as fluid on baseline and all study visits through week 12

retinal fluid status at weeks 12 and 52.[25] Their data revealed that, compared with Rq4, the relative risk (95% confidence interval [CI]) of the presence of fluid at week 12 was 0.74 (0.63–0.88) for 2q4, 1.18 (1.03–1.36) for 0.5q4, and 0.80 (0.68–0.94) for 2q8. This implies that the higher dose of aflibercept had a lower relative risk of fluid but was similar for the 4- and 8-week groups. In patients with fluid at week 12, the unadjusted relative risks (95% CI) of not having fluid at week 52 (compared to Rq4) was 1.34 (1.08–1.67) for 2q4, 1.07 (0.86–1.33) for 0.5q4, and 1.34 (1.08–1.66) for 2q8. The higher-dose aflibercept groups, therefore, had better chance of no fluid, and the findings were similar for the 4- and 8-week groups. The presence of fluid, however, did not impact the mean change in vision from week 12 to 52. The unadjusted percentages of patients with fluid gaining 3 lines from week 12 to 52 were 32% (Rq4), 32% (2q4), 27% (0.5q4), and 30% (2q8). It is important to note that the fluctuation in the mean central retinal thickness over time seen with the aflibercept 2q8 dose was present regardless of presence of fluid at week 12.

Switching anti-VEGF agents

Several presentations discussed anatomic and visual outcomes in patients who were switched from one anti-VEGF therapy to another. Notably, as aflibercept has been available in the United States (US) for <2 years (not yet approved by Health Canada), all of the presented data included one-way switching; ie, from current standard of care ranibizumab or off-label bevacizumab to aflibercept. Preliminary data from these retrospective analyses indicated that switching AMD patients who have persistent fluid despite treatment with other VEGF inhibitors to aflibercept may result in anatomic, but not visual, improvements. In addition, most patients require treatment every 4–6 weeks.

Hyung Cho, MD, presented a retrospective chart review of patients with wet AMD and suboptimal response (ie, persistent retinal fluid despite a minimum of 6 monthly treatments) to ranibizumab 0.5 mg, bevacizumab 1.25 mg, or both, who were switched to aflibercept 2.0 mg.[26] From the initial pool of 353 eyes, investigators reviewed 28 eyes (28 patients). After a single aflibercept injection, 89% (25 eyes) showed anatomic improvement and 18% (5 eyes) were dry. Central subfoveal thickness improved significantly, from a baseline of 295 µm to 272 µm. At 6 months, the improvement was maintained at 274 µm (P=0.008). However, switching to aflibercept did not lead to improvement in VA despite the fact that after 6 months of treatment 64% of eyes showed anatomic improvement, and one-quarter of them were dry.

Theodore Leng, MD, MS, presented a retrospective analysis of patients at a single academic referral centre who were switched from ranibizumab (103 patients; average of 14.3 injections prior to switching) or from bevacizumab (27 patients; average of 11.9 injections prior to switching) to aflibercept (between November 2011 and February 2013).[27] They found no clinical difference in visual or anatomic outcomes.

In a third retrospective chart review, Ashish Sharma, MD, FACS, reported on 93 eyes from 83 AMD patients who, despite multiple injections of ranibizumab or bevacizumab (average 19 injections per eye [range 6–34]), presented with macular edema, subretinal fluid, or retinal pigment epithelial detachment.[28] After switching to aflibercept, anatomic improvement was seen in 20% of eyes, no change in 14%, and a worsening in 14% of eyes after 14 months; follow-up was insufficient in the remaining 10% of eyes. Average central foveal thickness improved from 368 µm at baseline to 297 µm at 1 month, and was sustained at 316 µm at 1 year. Notably, vision improved in 40% of the aflibercept-treated eyes, remained the same in about 30%, and worsened in 27%. Furthermore, upon extension of the treatment interval to 8 weeks, recurrence of previously resolved fluid was seen in 33 eyes.

Franco Recchia, MD, described achievement of dry macula in two-thirds of eyes with residual retinal edema despite previous anti-VEGF therapy (62 eyes from 57 patients; average of 17 previous anti-VEGF injections) after 12 months of aflibercept.[29] However, most of these patients required injections every 4–6 weeks to maintain dryness. Treatment was extended to every 8 weeks in fewer than 20% of patients.

An analysis of 42 eyes confirmed that eyes with wet AMD refractory to prior treatment with bevacizumab, ranibizumab, or both showed a statistically significant improvement in mean central foveal thickness after 3 consecutive aflibercept injections (from an average of 261 µm at baseline to 244 µm).[30] After 3 monthly loading doses, patients were treated prn and vision was stable over the 6-month study period.

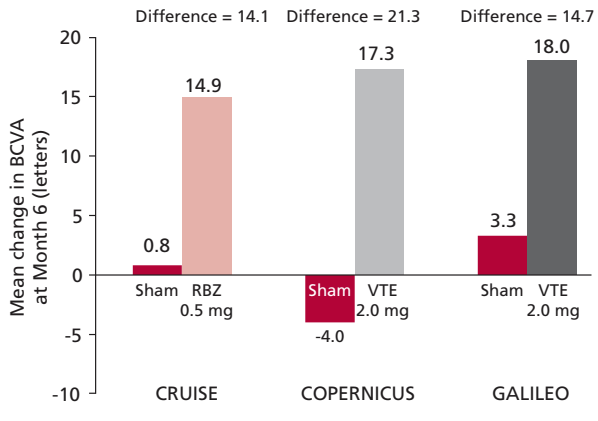
Finally, Eric Nudleman, MD, PhD, presented a retrospective analysis of 8 AMD patients who responded poorly to the aflibercept switch.[31] Upon switching to aflibercept, all patients reported subjective symptoms of decreased vision. BCVA had worsened by 1-2 lines, from a mean of 20/55 before injection to a mean of 20/64 after injection. Mean central macular thickness also increased by more than 70%. However, after being switched back to ranibizumab, all patients reported a subjective increase in vision and a return to their baseline VA.

Anti-VEGF Therapy for the Treatment of Retinal Vein Occlusion

According to a subanalysis of the COPERNICUS and GALILEO studies, the fluid status after 6 monthly injections of aflibercept is an important predictor of the future number of prn injections in patients with central retinal vein occlusion (CRVO), as presented by David Boyer, MD.[32] The COPERNICUS and GALILEO trials included a similar 6-month phase, during which patients were randomized to receive either aflibercept (2 mg) or a sham injection every month.[33] In a second 6-month phase of the GALILEO study, patients in the treatment group were treated on a prn basis with aflibercept, while patients in the placebo group continued with sham injections. In the second 6-month phase in the COPERNICUS study, all patients were treated prn with aflibercept. Aflibercept treatment led to an improvement in VA of ≥15 letters in 55.3% (COPERNICUS) and 60.2% of patients (GALILEO); however there was a modest decrease in VA gain from month 6 to month 12 with the switch to prn dosing. Mean numbers of injections between 6 and 12 months were similar in both trials and were dependent on fluid status at month 6.[32] There was an approximate 1.75-injection difference between dry and wet groups (2.64 vs 4.39 injections, respectively). Diabetes was also a significant factor that influenced number of treatments.

While acknowledging the limitations of cross-trial comparisons, Pravin Dugel, MD, compared published data from the sham-controlled CRUISE trial with ranibizumab and COPERNICUS and GALILEO trials with aflibercept.[34] Data from all 3 trials were statistically and clinically significant in favour of the treatment compared with sham (Figure 6). Six-month results were also comparable between drugs; a ≥15-letter gain was achieved by 48% of CRUISE patients, 56% of COPERNICUS patients, and 60% of GALILEO patients. It should be noted that the differences, as pointed out by Dr. Dugel, are likely due to inclusion criteria and patient baseline characteristics, which he emphasized when looking at how the sham-treated patients responded in these trials. Mean number of prn injections between months 6 and 12 were similar across the 3 studies with an average of 3 injections.

Figure 6: COPERNICUS and GALILEO trials: fluid status and diabetes as predictors of the number of aflibercept injections[32]

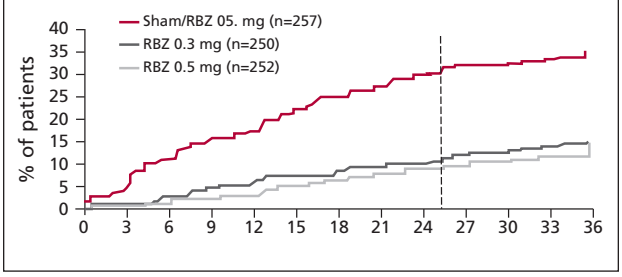


Diabetic Retinopathy (DR) and DME

Update on RISE and RIDE trials

RISE and RIDE are parallel, methodologically identical, Phase III, multicentre, double-masked, sham-controlled, randomized studies that assess the efficacy and safety of intravitreal ranibizumab (0.3 mg or 0.5 mg) in DME.[35] All patients received monthly injections for 2 years and participants in the sham group were eligible for crossover to 0.5 mg ranibizumab during the third year. Three-year data from these trials were presented by W. Lloyd Clark, MD.[36] Patients treated with ranibizumab had an approximately 3-fold lower risk of developing proliferative DR (Figure 7). Through 36 months, 33.9% of eyes originally randomized to sham developed proliferative DR, compared to 12.8% and 15.1% of 0.3 mg and 0.5 mg ranibizumab-treated eyes, respectively. The presence of baseline macular capillary loss was associated with DR progression in ranibizumab-treated eyes (P=0.0024). In the sham-treated group, severe baseline DR (P<0.0001) and the presence of subretinal fluid (P=0.04) were associated with DR worsening.

Figure 7: RISE AND RIDE Trials: time to development of proliferative diabetic retinopathy (PDR)[36]



Approximately 3-fold lower risk of PDR in ranibizumab-treated eyes

Anterior chamber cytokine levels and their association with disease severity in DME

Two presentations addressed the role of various cytokines in the pathogenesis of DME. David Wong, MD, FRCSC, demonstrated a statistically significant association between aqueous intercellular adhesion molecule 1 (ICAM-1), interleukin-10 (IL-10), and IL-6 and the severity of the disease determined by VA, macular volume (MV) and OCT measurements.[37] Rajeev Muni, MD, MSc, FRCSC, demonstrated that, in addition to lowering intraocular VEGF levels, treatment with ranibizumab also decreases levels of other anterior chamber cytokines, including ICAM-1, IL-6, PlGF, and monocyte chemotactic protein-1 (MCP-1).[38] Furthermore, ICAM-1 was found to be a predictor of the response to ranibizumab therapy. Treatment response was defined as reduction in MV of 10% (month 2 versus baseline).

Both presentations suggest that, in addition to VEGF, other cytokines play an important role in the pathogenesis of DME and predict subsequent therapeutic response to intravitreal

anti-VEGF therapy. Thus, specific modulation of anterior-chamber cytokine levels may provide therapeutic benefit to patients with DME.

Safety Update

Ranibizumab

Baruch Kuppermann, MD, PhD, presented the results of a large meta-analysis comparing the systemic safety data available for intravitreal ranibizumab.[39] The analysis included 14 Phase II and III clinical trials and 6504 patients representing 7544 patient-years. The investigators looked at 0.5-mg and 0.3-mg doses of ranibizumab versus sham, as well as 0.5 mg ranibizumab versus 0.3 mg ranibizumab, in the treatment of wet AMD, RVO, and DME. Prespecified endpoints included arterial thromboembolic events, death, fistulae, gastrointestinal perforation, non-central nervous system hemorrhage, hypersensitivity, hypertension, proteinuria, wound healing complications, and nonocular venous thromboembolic complications. No imbalances were observed in wet AMD or RVO for any of these prespecified systemic endpoints. The overall event rates were also low for DME and the majority of prespecified endpoints did not show an imbalance. However, numerical imbalances in pairwise comparisons were observed in rates of:

- Death for ranibizumab 0.3 mg versus control (sham/laser).
- Death, stroke, and wound healing complications for ranibizumab 0.5 mg versus control (sham/laser)
- Stroke for ranibizumab 0.5 mg versus ranibizumab 0.3 mg

It was pointed out that the imbalances in rates for ranibizumab in death and stroke were observed in the second year of treatment, where data consisted only of RISE and RIDE studies in which ranibizumab was administered monthly for 2 years.[35] Independent of treatment, DME patients with certain comorbidities were at higher risk for serious AEs. For example, patients with prior stroke had a higher risk of stroke. Overall, events rates were low for all groups and consistent with the known safety profile of ranibizumab.

Noted limitations of this meta-analysis include inclusion of patients with different dosing frequencies and concomitant therapies (some patients received photodynamic therapy). Additionally, the studies varied by design, risk factors, definition of systemic endpoints, data collection, patient population, inclusion and exclusion criteria and region. Evaluation of infrequent systemic adverse events can be also difficult as these events are also seen in the target patient populations (ie, the elderly and patients with diabetes).

Suber Huang, MD, MBA, discussed the risk of sustained elevation in intraocular pressure (IOP) with intravitreal ranibizumab in patients with DME.[40] As per the Diabetic Retinopathy Clinical Research Network Phase III trial protocol,[41] eyes with DME and IOP ≤24 mm Hg were randomly assigned to sham with prompt laser (n=260) or ranibizumab with prompt or deferred laser (n=322). During the first year of the study, all eyes were assessed every 4 weeks with IOP values obtained at each visit. After year 1, patients were evaluated every 4 months. Throughout year 1, persistent IOP elevation or initiation of ocular antihypertensive medications was noted in 10 (4%) patients in the sham group versus 20 (7%) in the ranibizumab group (hazard ratio [HR] 1.6, 95% CI: 0.8–3.5). However, throughout 3 years of treatment, a significantly higher percentage of ranibizumab treated patients experienced an increase in IOP or required treatment (14% versus 7%; HR 1.9, 95% CI 1.1-3.3; *P*=0.03).

These data indicate that intravitreal injections of ranibizumab for centre-involved DME are unlikely to increase the risk of sustained elevation of IOP or require antihypertensive medications for at least 1 year. However, the higher incidence of increase in IOP observed in ranibizumab-treated patients throughout 3 years is noteworthy and likely requires further investigation.

Aflibercept

Several presentations discussed the frequency and characteristics of sterile intraocular inflammation occurring after intravitreal aflibercept. In a retrospective case series that evaluated 4867 aflibercept injections (November 2011 through December 2012) at a single large retina group practice, Deborah Chong, MD, reported that the incidence of sterile intraocular inflammation was 0.33% (16 of 4867 injections).[42] The average time between injection and onset of symptoms (typically floaters or blurred vision with minimal pain) was 1.9 days. The ASRS task force, however, reported rates of about 0.05% (15 reported events in ~30 000 injections within 3 months of the drug approval).[43] This is similar to rates observed with ranibizumab (0.02% to 0.10%) in the ANCHOR,[21] MARINA,[22] and CATT[13,44] trials.

Conclusion

The quest to better understand the pathophysiology of retinal disease and to find better treatment approaches continues. We have come a long way over just a few years and have reached the point where it is possible to reliably stop the progression, and even improve the vision, in patients with AMD, DME, and RVO. The reports reviewed in this article from the ASRS meeting suggest that our current anti-VEGF strategies are safe and can improve visual function in our patients. They also illustrate that our current treatment strategies still have deficiencies for those patients with only partial therapeutic responses. As we learn more about the molecule-specific mechanisms of disease in AMD, DME, and RVO, including the role of VEGF in conjunction with other inflammatory mediators, our therapeutic approaches will evolve and become more targeted. It is conceivable that our current individualized treatment approach will also evolve in a similar way as we may have the capability to tailor our choices of therapy to the particular molecular or cytokine profile for each individual patient, which will improve outcomes even further.

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