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Retina-related Highlights from WOC and COS

A Review of Presentations at the World Ophthalmology Congress

June 5 – 8, 2010 Berlin, Germany

Originally presented by: L. Aiello, MD; G. Lang, MD; and P. Mitchell, MD

and the

Canadian Ophthalmological Society Meeting

June 26 – 29, 2010 Quebec City, Quebec

Originally presented by: E. Tourville, MD; D. Wong, MD; B. Leonard, MD; G. Katz, MD; P. Kertes, MD; J. Kent, MD; T. Sheidow, MD; D. Chow, MD; P. Hooper, MD; and E. Chew, MD

Reported and discussed by:
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June 2010 marked 10 years since verteporfin photodynamic therapy (PDT) – the first pharmacotherapeutic agent for the treatment of wet age-related macular degeneration (AMD) – was approved in Canada. Since then, significant strides have been made in the management of AMD, in treatment options for other ocular diseases (ie, diabetic macular edema [DME]), and in our knowledge of the genetics and pathogenesis behind these eye diseases. Other studies have shed light on the importance of the dietary intake of vitamins and antioxidants in influencing ocular health. These topics and others were presented at this year's World Ophthalmology Congress (WOC) in Berlin and the annual meeting of the Canadian Ophthalmological Society (COS) in Quebec City, and form the basis for this issue of *Ophthalmology Scientific Update*.

Update on Treating DME from the WOC

Although there are some limitations to using laser focal/grid photocoagulation to treat DME, some common misconceptions have been disproved in recent studies. For example, it is now known that laser therapy is better for treating DME than intravitreal steroids, that it can be used in patients with thicker retinas, and that multiple treatments are possible, if needed. Laser photocoagulation can also lead to improvements in visual acuity (VA) for many patients. However, there are data indicating that laser photocoagulation has limited use as monotherapy. Michaelides et al[1] compared patients receiving off-label bevacizumab at baseline, week 6, and week 12 to those receiving laser photocoagulation at weeks 16, 32, and 48. They reported that 31% of the patients treated with bevacizumab gained ≥10 letters of VA compared with 7.9% of those treated with laser. In addition, more patients treated with bevacizumab lost ≤15 letters and had greater reductions in central macular thickness.

In an ongoing Phase III study[2] of patients treated with pegaptanib 0.3 mg or a sham for 1 year, followed by laser photocoagulation for an additional year, pegaptanib/laser was superior to sham/laser, although the outcomes were less remarkable (ie, improvements in VA of 5.2 and 6.1 letters at 1 and 2 years, respectively). The risk of significantly elevated intraocular pressure (IOP) was also greater in patients treated with pegaptanib.

The Diabetic Retinopathy Clinical Research Network (DRCR.net)[3] investigated 691 patients (854 eyes) treated with early laser therapy (given within 1 week of diagnosis) or with delayed laser therapy (given >24 weeks after diagnosis) plus intravitreal triamcinolone (IVTA) 4 mg, ranibizumab 0.5 mg, or a sham injection. After 1 year, patients treated with ranibizumab experienced improvements in VA of approximately 9 letters (P<0.001) compared with those treated with sham/prompt laser (~3 letters). Patients treated with IVTA/prompt laser showed improvements of ~6 letters during the first 4–6 months, but this improvement was lost over time and, at 1 year, outcomes were

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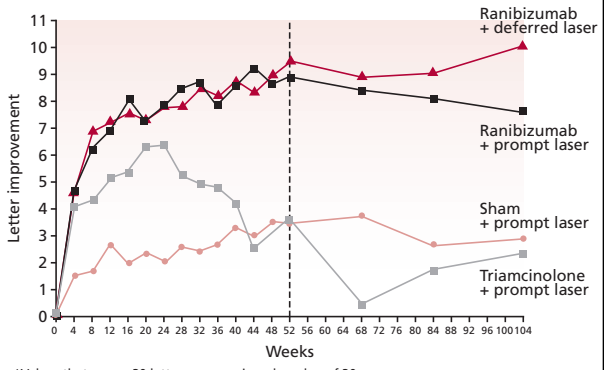
Figure 1: Mean change in visual acuity after 1 year of treatment with early laser, delayed laser, delayed laser plus IVTA, ranibizumab, or sham injection[3]



*Values that were ±30 letters were assigned a value of 30

P-values for difference in mean change in visual acuity from sham+prompt laser at the 52 week visit: ranibizumab+prompt laser <0.001; ranibizumab+deferred laser <0.001; and triamcinolone+prompt laser=0.31.

no better than with the sham treatment (Figure 1). Subgroup analyses revealed no clinically important results according to the patient's degree of DME at baseline, prior DME treatments, baseline VA, or baseline central subfield thickness. This study reported a higher than expected rate of endophthalmitis among patients treated with ranibizumab (cumulative risk = 1% per patient at 2 years). There was no increased risk of cardiovascular events. Almost half of those treated with IVTA experienced a significant increase in IOP after 2 years and 54% had an increased risk of cataract surgery after 2 years.

There is a pressing need for new treatments for DME since 6%–10% of patients with diabetes mellitus have clinically significant DME. As a result, approximately 3.5 million diabetics worldwide have significant vision loss. In a small Phase II study (RESOLVE), 151 patients were treated with ranibizumab (0.3 mg or 0.5 mg) for 3 loading doses, followed by as-needed (PRN) retreatments, or sham injections. Patients receiving ranibizumab were allowed to have a double-dose after the first injection if it was deemed necessary. Over the 12-month period, patients who began treatment with ranibizumab 0.3 mg received a mean of 4.4 injections at the initial dose and a mean of 5.8 injections at 0.6 mg, while those who began treatment with ranibizumab 0.5 mg received a mean of 4.9 injections of the lower dose and a mean of 5.2 injections at 1.0 mg. VA improved by a mean of 10.3 letters from baseline (pooled results) for ranibizumab-treated patients, compared with a mean loss of 1.4 letters for those who did not receive additional care. Mean reductions in central retinal thickness (CRT) were 194 µm for patients receiving ranibizumab compared with 48 µm for those receiving usual care. Two patients in the study groups developed endophthalmitis and 3 developed arteriothrombotic events.

A larger Phase III multicentre study (RESTORE) enrolled 345 patients, including subjects at 6 sites in Canada. The study compared ranibizumab 0.5 mg alone, ranibizumab 0.5 mg plus laser photocoagulation, and laser monotherapy. Ranibizumab was given at baseline and at months 1 and 2, while laser was given at baseline, then every 3 months thereafter if needed. After 1 year, there was little difference in changes in VA between the groups receiving ranibizumab alone and those receiving ranibizumab plus laser (6.1 versus 5.9 letters, both $P<0.0001$), whereas patients receiving laser monotherapy gained on average <1 letter. Approximately 40% of the patients receiving ranibizumab achieved gains in VA of ≥10 letters, while 20% of those treated with laser monotherapy lost 1 to 15 letters. Virtually all of the gains in VA observed in patients receiving ranibizumab occurred within the first 3 months. Several subgroup analyses revealed that there were no differences in outcomes according to CRT at baseline, whether the DME was focal or diffuse, or whether the patient had had prior laser treatments.

This study concluded that ranibizumab was well tolerated, either as monotherapy or in combination with laser. There were no unforeseen nonocular adverse events (AEs). The most common ocular AE was subconjunctival hemorrhage (7%–8% of patients receiving ranibizumab), but in none of those treated with laser alone.

Discussion about laser/DME continued at the annual COS meeting.

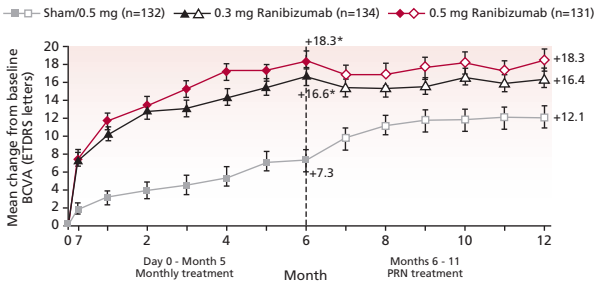
As Eric Tourville, MD, FRCSC, from Université Laval advised, "there is still a lot of use for lasers." While DME patients treated with IVTA 4 mg can achieve a "dramatic" increase in VA within the first few months of treatment, this benefit may disappear within a year. Laser therapy, on the other hand, has been shown to have a more lasting benefit.[4] In fact, laser photocoagulation appears to be a superior option regardless of cataract status and whether the eye is pseudophakic or not. As for prompt versus delayed laser therapy, there is virtually no difference between laser/sham and laser/IVTA (gains of 3 and 4 letters, respectively). Moreover, 2-year data have recently revealed that gains achieved with either ranibizumab/laser or laser alone were maintained out to 2 years, whereas all of the gains observed with laser/IVTA were lost by the end of 2 years.

Laser continues to play an important role in the management of DME. IVTA should not be used as monotherapy, but only in combination with laser photocoagulation. When IVTA is used, 1 mg should be the maximum dose, especially with pseudophakic patients. Ranibizumab and off-label bevacizumab are both superior to laser alone and both are better than laser/IVTA in pseudophakic patients. Vitrectomy still has a role to play in treating DME, although in general outcomes are not as favourable as those observed with either of the anti-vascular endothelial growth factor (anti-VEGF) treatments.

Treating Retinal Vein Occlusions

Seventy-four per cent of patients who develop branch retinal vein occlusion (BRVO) spontaneously recover approximately 2 lines of VA within 6 months. At 12 months, the mean recovery is around 1.7 lines.[5] Macular edema is a concern, however, affecting approximately 5% of patients at 6 months and 15%

Figure 2: Results of the BRAVO Study – Mean change from baseline best corrected visual acuity over time to 12 months[6]



*P<0.001 vs. sham. Earliest statistically significant group difference (P<0.0001 vs sham) was at Day 7. Vertical bars are ±1 standard error of the mean. P values for 0.3 mg and 0.5 mg groups vs. sham/0.5 mg at Month 12 were not calculated.

The last-observation-carried-forward method was used to impute missing data.

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

within 12 months, with <20% experiencing any kind of spontaneous resolution. The BRAVO study,[6] presented at the recent WOC, revealed that patients treated with monthly ranibizumab 0.3 mg or 0.5 mg gained 16.4 and 18.3 lines of VA, respectively, over a 6-month period (Figure 2). These gains were maintained virtually unchanged out to 12 months. Patients who were initially treated with sham injections had a mean gain in VA of 12.1 letters at the end of follow-up. BRAVO also revealed significant improvements in central foveal thickness (CFT), averaging around 340 µm.

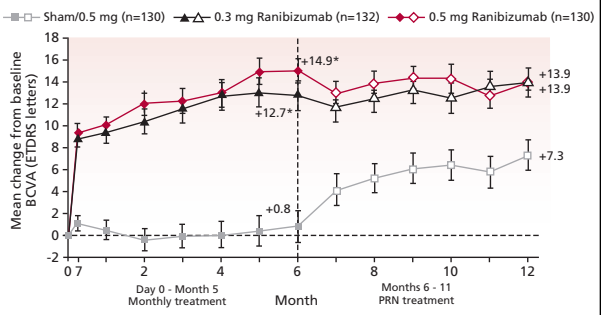
To date, the standard of care for BRVO has been grid laser photocoagulation. The SCORE study[7] followed 411 patients treated with IVTA 1 mg, IVTA 4 mg, or laser photocoagulation, every 4 months. No significant differences were found between any of the arms in VA improvements from baseline, changes in centre-point thickness, or in the percentage of patients showing a ≥15 letter gain in VA. Adverse events, including spikes in IOP to ≥35 mm Hg, were more common in the 4 mg IVTA group compared with either of the other 2 arms. On the basis of these data, laser should remain the standard of care for patients with BRVO.

Injectable biodegradable implants containing 0.7 mg of dexamethasone are not yet available in Canada. In a study by Haller et al,[8] statistically significant gains were demonstrated in VA from baseline at 30, 60, 90 and 180 days. Sixteen percent of patients also developed spikes in IOP to ≥25 mm Hg.

A survey by the American Society of Retinal Specialists has found that >50% of its members now use anti-VEGF blockade to treat central retinal vein occlusion (CRVO). However, anti-VEGF injections have some important limitations: they require repeat injections, do not promote reperfusion of the underlying pathology, and there is some suggestion that they could impede reperfusion.

Nonetheless, data from the CRUISE study presented at the WOC and published just days before the COS meeting[9] offer a more positive view of anti-VEGF drugs. This Phase III study was similar to the BRAVO study and followed 392 patients with ME secondary to CRVO. They received 6 monthly injections of ranibizumab (0.3 mg or 0.5 mg) or monthly sham injections.

Figure 3: The CRUISE Study– Mean change from baseline best corrected visual acuity with different regimens over time to 12 months[9]



*P<0.001 vs. sham. Earliest statistically significant group difference (P<0.0001 vs sham) was at Day 7. Vertical bars are ±1 standard error of the mean. P values for 0.3 mg and 0.5 mg groups vs. sham/0..5 mg at Month 12 were not calculated.

The last-observation-carried-forward method was used to impute missing data.

Ranibizumab retreatments were offered PRN for a further 6 months. At 6 months, mean changes in VA from baseline were 14.9, 12.7, and 0.8 letters for patients in the 3 arms, respectively (Figure 3). Improvements in ranibizumab-treated patients were mainly unchanged over the following 6 months (final VA = 13.9 letters in both groups). Patients treated with the sham achieved an improvement in VA of 7.3 letters from baseline to month 12. Mean CFT decreased by 452 µm in the ranibizumab 0.5 mg arm and by 434 µm in the ranibizumab 0.3 mg arm at 6 months follow-up. Direct comparisons of outcome data between the sham and ranibizumab arms were not made because of incomplete data for sham patients during the maintenance phase.

In both CRVO studies, patients treated with intravitreal ranibizumab experienced rapid and dramatic improvements in CFT and VA within 7 days of their first injection. Patients receiving the sham treatments also experienced improvements in VA and CFT, but gains were slow and gradual and not as great as those seen in the ranibizumab arms. Also, although patients who were initially assigned to the sham treatment achieved clinically important improvements in VA once they were started on ranibizumab, these gains did not match those observed in patients who began ranibizumab treatments earlier. This suggests that earlier treatment results in greater gains in VA and that delayed treatment may be detrimental since the longer VA is lost, the harder it is to recapture it.

A controversial treatment for non-ischemic CRVO employs a high-intensity laser to puncture Bruch's membrane and create a chorioretinal anastomosis. This is used to create a bypass channel that enables venous blood to enter the choroid, bypassing the site of the occlusion and leading to decompression of the obstructive retinal venous circulation. The technique was pioneered 15 years ago in Australia,[10] but was associated with a high rate of adverse events. Brian Leonard, MD, FRCSC, and colleagues at the Ottawa Eye Institute have developed a modified technique that uses a lower-intensity laser with a longer duration of exposure. During 48 months of follow-up, VA improved by

1–11 lines (mean improvement 5 lines) in 16 of 19 eyes; no change was recorded in 3 of the 19 eyes. They are now attempting to combine the procedure with anti-VEGF therapy since it is possible to get an anastomosis and to protect the macula using a combination of VEGF-α inhibition with this modified laser technique.

The Canadian experience

VEGF blockade

Although VEGF inhibitors are the gold standard for treating AMD in Canada, Canadian ophthalmologists may not be achieving the same outcomes with these drugs as colleagues in other countries. Peter Kertes, MD, FRCSC, of the Sunnybrook Health Sciences Centre compared outcomes in patients treated with ranibizumab at 3 retinal practices in Canada against data from 3 multicentre trials that have dictated ranibizumab use worldwide (MARINA,[11] ANCHOR,[12] and PrONTO[13]).[14] Canadian physicians often cite these findings when advising that one-third or more of their patients may expect significant gains in VA and that the vast majority will not lose this VA gain. Based on the PrONTO study data, Canadian patients are being told that outcomes from intermittent treatment schedules are comparable to what is seen with monthly injections; however, these results have not been replicated in these Canadian practices.

In a retrospective chart review of 94 patients (with 95 treatment-naïve eyes) treated at 3 practices in Toronto and for whom 1 year of follow-up was available, the mean VA scores improved from 20/100 at baseline, to 20/77 at 3 months, and 20/74 at 6 months. However, there was a slight decline to 20/83 at 12 months. Eyes with a baseline VA of <20/320 had the best outcomes, with a mean improvement in VA of 16.5 letters. On the other hand, eyes with a baseline VA between 20/40 and 20/320 (the parameters used in the MARINA and ANCHOR trials) had a mean loss of 2.5 letters at 12 months. Furthermore, in each of the 3 major trials, >90% of patients lost ≤15 letters, compared with 82% of patients in the Sunnybrook review. While MARINA, ANCHOR, and PrONTO reported that 33.8%, 40.3%, and 35% of patients in each of the ranibizumab arms, respectively, gained ≥15 letters in VA (Figure 4), only 25% of these Canadian patients achieved this kind of improvement. Among patients whose baseline VA was <20/320, 46% gained at least 3 lines of VA. Possible explanations for the differences in results include:

- Optical coherence tomography (OCT) was not funded by Ontario's universal healthcare plan at the time of the study. Patients had monthly OCT exams in PrONTO, while Sunnybrook patients had a mean of just 3.5 OCT exams over 12 months of follow-up. This less rigorous surveillance could have resulted in poorer outcomes.
- Patients at Sunnybrook had a mean of only 1.4 injections during the second 6 months of follow-up, fewer than what was seen in PrONTO. Although PrONTO showed that gains in VA could be maintained when PRN dosing followed an induction phase of at least 3 injections, outcomes were even better when monthly dosing was given.
- The Toronto winter weather may have kept many patients away from the clinic, so they received fewer injections overall. This could also explain the loss of VA during the second 6 months of treatment that began in October.

OCT is now a universally insured service in Ontario and this may impact future outcomes because closer monitoring should lead to greater VA stabilization and, it is hoped, less loss of previously gained VA. As a result of this study, clinicians should offer patients a more realistic sense of what may be expected from anti-VEGF treatments.

Monthly versus intermittent dosing of ranibizumab

Gabriel Katz, MD, of St. Michael's Hospital discussed monthly versus intermittent dosing with ranibizumab. In a chart review of patients who received either 12 monthly ranibizumab injections or 3 loading doses followed by PRN re-treatments, patients in the intermittent dosing group received a mean of 8 injections over 12 months. Patients in both groups experienced significant gains in VA within the first 4 months and, although between-group differences at the end of 12 months favoured monthly dosing, the difference was not statistically significant (P=0.53). There was no significant difference in the per-

Figure 4: A comparison of results with ranibizumab in MARINA, ANCHOR, and PrONTO[14]

	MARINA	ANCHOR	PrONTO	All eyes	20/40 - 20/320	<20/320	>20/40
Eyes that lost <15 letters (%)	94.6	96.4	95	82	75	93	100
Eyes that gained ≥15 letters (%)	33.8	40.3	35	25	11	46	0
No. of injections	12	12	5.6	5.2 ± 2.85	5.0 ± 2.80	5.4 ± 3.16	5.5 ± 2.07
No. of follow-up visits	12	12	12	9.4 ± 2.27	9.3 ± 2.38	9.4 ± 1.94	10 ± 2.76
No. of OCTs per patient	n/a	n/a	12	3.5 ±2.66	4.0 ± 2.92	2.3 ± 1.76	4.2 ± 1.47

OCT, optical coherence tomography

centage of patients who lost or gained ≤3 lines of VA, nor was there a significant difference in changes in CRT between the 2 groups. This suggests that both treatments may be beneficial, but it does not mean that one treatment is superior to the other. Patients should be offered the option of having either monthly or intermittent treatments when planning their treatment regimens and they should be informed that monthly dosing has been shown in trials (eg, SUSTAIN[15] and EXCITE[16]) to provide better overall improvements in VA and that such improvements are maintained over longer periods.

Switching from bevacizumab to ranibizumab

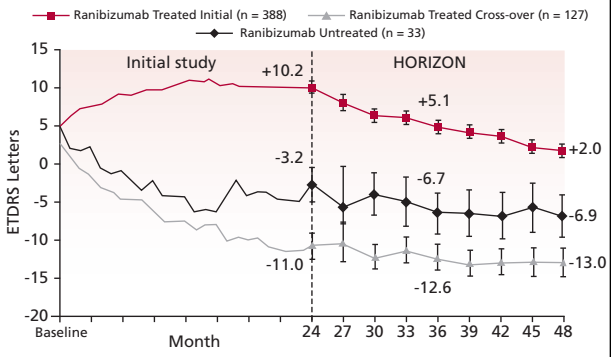
In March 2008, when the Ontario Drug Benefits program began to cover the cost of ranibizumab, many patients previously treated with off-label bevacizumab switched to ranibizumab. According to Jerrod Kent, MD, a resident at the Ivey Eye Institute in London, this provided a fortuitous opportunity to see what the impact might be when patients switch from one medication to another within the same class of drugs. Overall, there was no significant difference in VA outcomes with either VEGF blocker. However, in a subgroup analysis, those who received ≥3 prior injections of bevacizumab before switching to ranibizumab had an additional improvement in VA from 20/77 to 20/66 (P=0.009). Change in VA for those who had received ≤2 prior injections of bevacizumab was not clinically or statistically significant. A statistically significant difference in the best VA recorded was observed when patients were switched to ranibizumab: 0.63 logMAR with bevacizumab versus 0.45 logMAR with ranibizumab (Snellen equivalent 20/85 and 20/57, respectively; P<0.0001). Mean retinal thickness was significantly improved in each subgroup, as well as for the study population as a whole, when patients switched to ranibizumab.

Outcomes were statistically significant in favour of ranibizumab treatment in 4 of the 5 parameters measured in this review; ie, VA in subgroups receiving <3 and ≥3 injections of bevacizumab, and retinal thickness in all patients and in the 2 aforementioned subgroups. This superiority could be attributed to patients receiving more injections of ranibizumab (mean 5.38) over a longer period of time (mean 515 days) compared with bevacizumab treatment (mean 3.84 injections over 329 days).

Current and Emerging Treatments for AMD

Tom Sheidow, MD, FRCSC, also of the Ivey Eye Institute, began by recapping the MARINA and ANCHOR studies, which demonstrated that intravitreal injections of ranibizumab not only controlled the advance of choroidal neovascularization, but also produced meaningful improvements in VA in approximately one-third of patients. The question is: What can be done to get the other two-thirds to improve? Although these 2 pivotal studies demonstrated significant gains in VA within the first 3 months, improvements were more gradual over the ensuing 9 months. It is also important to bear in mind that 6%–7% of patients had an initial loss of VA within the first 3 months, but

Figure 5: The HORIZON Study – monthly versus PRN dosing of anti-VEGF drugs[17]



showed a gain by the end of 12 months. Therefore, not everybody gets better within the first 3 months. The use of combination therapies and varied dosing schedules represent evolving treatment options, which prompts the question of what the optimal treatment duration should be.

The HORIZON study[17] demonstrated that when patients are treated with monthly dosing for 2 years and then switched to PRN dosing, initial gains in VA declined markedly over the next 2 years (Figure 5). Similarly, the EXCITE study compared monthly ranibizumab against 2 different doses given quarterly and showed that monthly dosing was superior (gains of 8.3 letters at 12 months vs gains of 4.9 and 3.8 letters in the 2 quarterly dosed arms) (Figure 6).

Although the primary endpoint of the SUSTAIN study was the safety of ranibizumab over a 1-year timeframe, it also demonstrated that intermittent, PRN dosing can be effective. SUSTAIN involved 513 ranibizumab-naïve patients who received 3 initial monthly doses of the drug (0.3 mg or 0.5 mg) followed by criteria-based PRN dosing for a further 9 months (Figure 7). The mean improvement in VA was 5.8 letters after 3 months (ie, during the loading phase) and 3.6 letters at the end of the study. The mean improvement in CRT over this time

Figure 6: EXCITE– Mean visual acuity change from baseline with different regimens of ranibizumab[16]

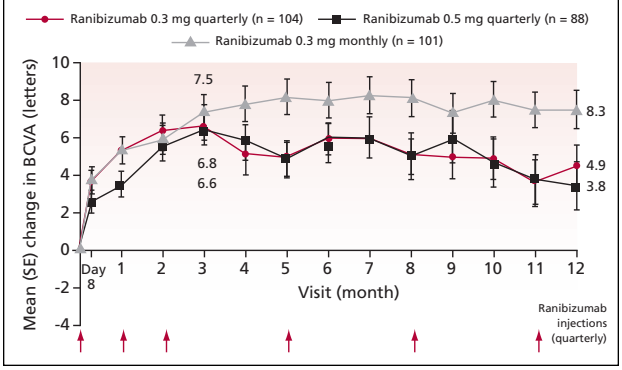
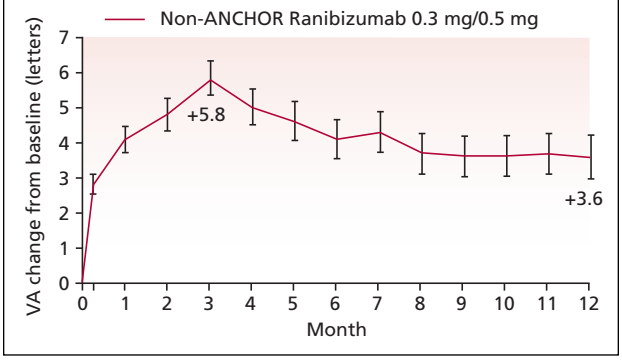


Figure 7: SUSTAIN – Mean best corrected visual acuity change in ranibizumab-naïve patients over 12 months[15]



period was 91.5 µm, which was considered to be "very substantial improvements." An analysis of the safety data reported a total of 41 AEs that were believed to be related to the study drug, including 19 cases each of hypertension and arteriothrombotic events. There were 6 cases of serious ocular AEs, including 2 retinal hemorrhages and one each of cataract formation, retinal pigment epithelial tear, loss of VA, and vitreous hemorrhage. Overall, the ocular safety profile seen in the SUSTAIN trial was similar to that seen in other phase III trials, including MARINA, ANCHOR, PIER, and EXCITE. Besides demonstrating the ocular safety of ranibizumab, the SUSTAIN study concluded that an initial loading phase of 3 monthly injections of ranibizumab is optimal and that individualized treatments using criteria-based PRN dosing can be effective. However, patients generally lost some of the VA they had gained during the loading phase when they switched to PRN dosing. Thus, it may be worthwhile to consider continuous monthly dosing when possible.

The issue of combination therapies is coming into better focus. Data from the DENALI study, presented at the recent WOC, suggest that monotherapy is actually superior to combination therapy when patients are treated with monthly ranibizumab compared with ranibizumab and either reduced-fluence or standard-fluence PDT as the first treatment. This may have implications for how therapy is delivered in Canada since, in the DENALI study, patients in the standard-fluence PDT arm received a mean of 2.2 injections in the PRN phase and 5.1 treatments over 12 months, substantially more than what patients received in the reduced-fluence PDT arm or the ranibizumab/sham PDT arm. When healthcare payors examine the DENALI results, there will be an opportunity to compare outcomes and cost analyses and see whether there is a meaningful difference.

Although bevacizumab is not approved for the treatment of AMD in Canada, it is here to stay, according to Dr. Sheidow. A recently published, prospective, randomized, controlled trial[18] which, although it employed outdated criteria (ie, pegaptanib was considered the standard of care when the trial was designed), showed "proof of concept" with 32% of bevacizumab-treated patients gaining ≥15 letters. No ocular AEs were detected that had not already been seen in other studies: 2 of 65 patients experienced a myocardial infarction with bevacizumab, one of whom died, whereas no events occurred in the pegaptanib or PDT arms.

The newest player in the field is VEGF-trap inhibition. In an unpublished study,[19] this therapy demonstrated significant gains in VA over baseline, with significantly fewer injections required during a 9-month PRN phase. Two Phase III controlled, double-masked studies, are underway to compare 3 different regimens with a VEGF-trap inhibitor against monthly ranibizumab monotherapy.

In the anti-VEGF Pipeline

A relative newcomer to the anti-VEGF field is aflibercept, commonly known as VEGF-Trap, a recombinant fusion protein that comprises sections of the human VEGF receptors 1 and 2, fused with the Fc domain of human immunoglobulin G. In a phase II study (CLEAR-IT), presented at the recent WOC, 2 cohorts of patients received the drug, either monthly for 12 weeks (ie, 4 doses) or at baseline and then at 12 weeks (2 doses). PRN dosing was offered for a further 40 weeks. The CLEAR-IT study reported that patients who received 2 mg in 4 loading doses followed by PRN dosing for a further 9 months, achieved a mean increase in VA of 9 letters ($P<0.0001$ compared with placebo). The study was then extended for a further 12 months during which the patients were offered open-label PRN dosing at 2 mg. During this extension period, the mean improvement in VA from baseline was 7.1 letters at 18 months and 6.1 letters at 24 months. Over this 21-month period of PRN dosing, patients received a mean of 4.6 additional injections on top of their induction phase injections; this translates into a mean of 1 injection every 4.6 months.

The VEGF-Trap experience has been expanded into 2 separate phase III studies: VIEW-1 that has enrolled 1217 patients in Canada and the United States, and VIEW-2 that has enrolled 1240 patients in the rest of the world. Patients will receive either 0.5 mg or 2.0 mg monthly for 24 months, or 3 loading doses at 2.0 mg, followed by 2.0 mg every 8 weeks for 2 years. These will be compared against a cohort receiving 0.5 mg of ranibizumab monthly for the same follow-up period. The primary endpoint will be the percentage of patients losing ≤15 ETDRS letters.

Genetics and Dry AMD

In addition to extensive presentations on wet AMD at the WOC and COS, there were also discussions about the management of dry AMD. David Chow, MD, of the University of Toronto stated that research into identifying patients who might develop dry AMD or might convert from dry to wet disease is still in the very early stages. At present, the Amsler grid – once the cornerstone of early detection – is thought to be unreliable in many cases. Spectral domain OCT is being used more frequently and can develop highly accurate pictures of changes in

retinal thickness and retinal pigment epithelium elevations. Its main limitation is that it detects changes after they have occurred and is not predictive of future disease. However, it is useful for monitoring patients with existing retinal disease and their response to therapy.

Preferential hyperacuity perimetry (PHP) is an in-office test that is 10 times more sensitive than standard VA testing and offers 82% sensitivity compared with the 8% sensitivity seen with the Amsler grid. However, the real future for dry AMD surveillance may be in genetic testing. "Macula risk," an in-office, saliva-based, genetic screening method, tests for 11 well-identified single nucleotide polymorphisms (SNPs). It also incorporates data on the patient's history of smoking and obesity and calculates the patient's risk of developing AMD.

Dr. Chow suggested that children and siblings of patients with AMD be tested. In addition, patients who currently have dry AMD should be tested regularly in order to more accurately predict their risk of progressive disease and vision loss. Patients identified at high risk could be counselled about lifestyle modifications (obesity, smoking, and dietary concerns), and surveillance could be stepped up so any degree of conversion might be detected earlier. Two recent studies have used genetic phenotyping to identify subgroups of patients who are less likely to respond to bevacizumab[20] and PDT.[21]

Managing Uveitis

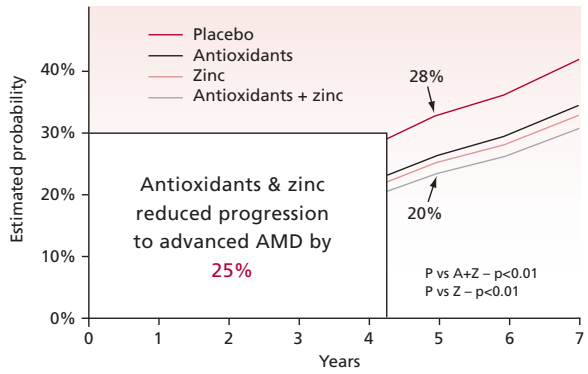
According to Phil Hooper, MD, FRCSC, also of the Ivey Institute, many unanswered questions remain about the treatment of posterior uveitis, including whether systemic therapy preserves vision better than local therapy, which systemic therapy is most effective, and which is the best way to treat cystoid macular edema (CME). An unpublished study[22] of 9250 patients reported that methotrexate, azathioprine, mycophenolate mofetil, cyclosporine A, and cyclophosphamide can each help around one-third of patients reduce their use of steroids and lead to immune suppression in 20%–65% of patients. Cyclophosphamide was the most effective treatment, but it also had the highest rate of discontinuation due to adverse events. Tumour necrosis factor alpha blockers (ie, infliximab) used off-label, may help one- to two-thirds of patients reduce or eliminate steroid use and are associated with an 80% remission rate at 6 months; this decreases to approximately 70% at 1 year. The downside to these drugs is that their safety profile remains unknown, as is the question of when they should be discontinued.

A relatively new local treatment is the fluocinolone implant. In a 2-year study, this implant was compared with "usual care", showing no difference in time to recurrence. There was a greater reduction in the incidence of CME (75% versus 65%). However, there was also a significantly higher risk (55% vs 10%) of developing elevated IOP. The question remains: Does good long-term local control beat systemic treatment in terms of the long-term disease outcome? Several ongoing randomized studies are investigating newer therapies (eg, voclosporin, adalimumab, and dexamethasone intravitreal implants) for the management of uveitis. A 28-week, phase III trial at 4 sites in Canada is now underway and will compare 3 doses of subcutaneous AIN457 against placebo in the treatment of posterior and panuveitus.[23]

The AREDS studies – Does Diet Help Prevent AMD?

This year, the E.A Baker lecture at the COS was presented by Emily Chew, MD, Deputy Director of Epidemiology and Clinical Research at the National Eye Institute in Bethesda, Maryland. She summarized the first stage of the well-known age-related eye disease study (AREDS),[24] which reported that supplements containing vitamins C, E, and beta carotene, plus zinc, led to a 25% reduction in the risk of progressing from moderate to severe macular degeneration over a 5-year period (Figure 8). Despite the AREDS findings, however, there is no known primary prevention for AMD. Vitamin and antioxidant supplementation appear to be beneficial only in patients who already have either large drusen in both eyes or advanced AMD in one eye and are, therefore, at high risk of progression. Smokers, even if they are at higher risk, should not use these supposed sight-saving products due to the increased risk of cancer among smokers who take beta-carotene. At the same time, additional research has reported that dietary intake of products such as lutein and omega 3 fatty acids (ie, fish oils) may improve retinal health and might be associated with a reduced risk of developing AMD, geographic atrophy, or the formation of intermediate- or large-sized drusen.[25] AREDS II is recruiting only patients with large drusen or advanced AMD at enrollment. These patients (n=4203) will be randomized to receive either lutein/zeaxanthin or omega-3 fatty acids, or a combination of the 2 products, with or without the kinds of supplements and vitamins used in the original AREDS investigation. Results from the study are expected in late 2012.

Figure 8: AREDS – Dietary supplements contribute to a 25% reduction in the progression of macular degeneration over 5 years



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