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Diabetic Macular Edema: Current Management and Future Options

By Rajeev H. Muni, MD, MSc (Clin Epi), FRCSC, and Radha P. Kohly, MD, PhD, FRCSC

Diabetic macular edema (DME) is the leading cause of moderate vision loss in working-aged individuals in developed countries.[1-3] Strict blood sugar and blood pressure (BP) control remain the most effective interventions to date.[4,5] Until recently, macular laser photocoagulation (MPC) was the mainstay of treatment for DME. MPC reduces the risk of moderate vision loss by 50% (from 24% to 12%) at 3 years in patients with clinically significant macular edema as evidenced by the pivotal Early Treatment Diabetic Retinopathy Study (ETDRS), published over 25 years ago.[6-8] Nonetheless, a significant proportion of patients treated with MPC continued to lose vision, with 20% of patients losing ≥2 lines of vision at 2 years. Consequently, other treatment approaches have been considered, most notably intravitreal triamcinolone acetonide and intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents. This issue of *Ophthalmology Rounds* will review the results of clinical trials conducted with these therapies.

Intravitreal Triamcinolone (IVT)

IVT has been used extensively over the past decade, as off-label treatment for DME as well as for macular edema arising from other retinal disorders. IVT has been shown to have anti-inflammatory, antivascular permeability, and antiangiogenic properties.[9] Some of these actions may be mediated in part by a steroid-induced reduction in the secretion of VEGF. Over the past decade, IVT was used primarily as an adjunct to MPC in patients who were resistant to laser alone. Its benefit in reducing central macular thickness on optical coherence tomography (OCT) and corresponding improvements in visual acuity (VA) led investigators to hypothesize that IVT could potentially be considered as primary treatment for centre-involving DME.[9] However, in a recent Diabetic Retinopathy Clinical Research Network (DRCR.net) study in which IVT monotherapy was compared to MPC for centre-involving DME, it was demonstrated clearly that MPC remained superior in terms of VA gain when compared to IVT monotherapy.[10] However, this study did not have a combination arm, and it is plausible that the combination of IVT and focal/grid laser could be superior to laser alone. In theory, IVT could rapidly reduce macular edema, allowing for more effective laser treatment when the retina is less edematous; the long-term benefits of MPC may, in turn, further reduce the number of repeated IVT injections required. This was studied in a more recent DRCR.net paper involving intravitreal ranibizumab, where it was shown that in pseudophakic eyes, IVT with prompt laser is superior to laser alone (discussed in more detail below).[11,12]

Intravitreal Anti-VEGF Agents

Intravitreal anti-VEGF agents have revolutionized the management of numerous retinal disorders. Increased VEGF levels have been found in the vitreous and retina of eyes with diabetic retinopathy.[13] VEGF is known to increase vascular permeability possibly by increasing the phosphorylation of tight junction proteins.[14] Intravitreal anti-VEGF agents include pegaptanib, bevacizumab, and ranibizumab. Pegaptanib is a modified ribonucleic acid (RNA)-oligonucleotide (VEGF 165 aptamer), which inhibits the interaction of

FACULTY OF MEDICINE
University of Toronto

Department of Ophthalmology and Vision Sciences

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

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VEGF 165 with its receptor. Bevacizumab is a recombinant humanized monoclonal full-length antibody that neutralizes all active isoforms of VEGF-A. Ranibizumab consists of only the Fab portion of the antibody. Pegaptanib was the first anti-VEGF agent to show a potential benefit in patients with DME.[15] However, there has been more interest and promise with the pan-VEGF-A blockade of ranibizumab and bevacizumab. Another anti-VEGF agent, aflibercept, is a fully human, soluble, VEGF receptor fusion protein that binds all forms of VEGF-A, along with the related placental growth factor.

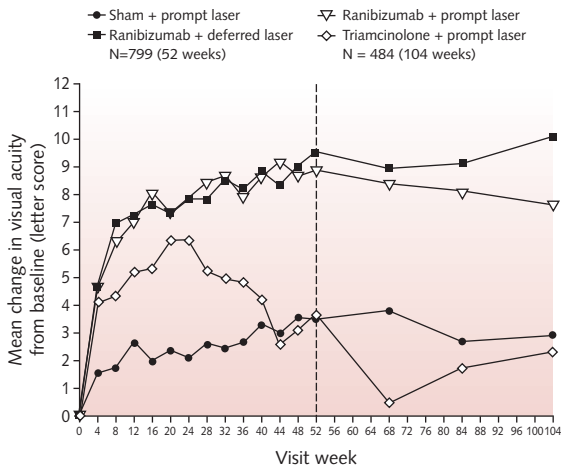
Review of Recent Randomized Clinical Trials for Ranibizumab in DME

DRCR.net trial

In the National Eye Institute-sponsored DRCR.net study,[11,12] 854 eyes of 691 participants with fovea involving DME with VA of 20/32 to 20/320 (approximate Snellen equivalent) were randomized to sham injection plus prompt laser (within 3-10 days after injection), ranibizumab 0.5 mg plus prompt laser, ranibizumab 0.5 mg plus deferred (≥24 weeks) laser, or triamcinolone 4 mg plus prompt laser. Patients were treated with repeated ranibizumab injections every 4 weeks for the first 12 weeks, after which a detailed retreatment algorithm was followed for the first year. Eyes in the triamcinolone group could receive repeated injections as often as every 16 weeks (with sham injections every 4 weeks). In the laser plus sham injection group, a retreatment algorithm was followed whereby patients could receive repeat laser provided at least 13 weeks had lapsed since the last laser treatment.

At 1 year, the investigators found that the mean change (± standard deviation [SD]) in the VA letter score from baseline was significantly greater in the ranibizumab plus prompt laser group (+9±11; $P<0.001$) and ranibizumab plus deferred laser group (+9±12; $P<0.001$), but not in the triamcinolone plus prompt laser group (+4±13; $P=0.31$), compared with the sham plus prompt laser group (+3±13) (Figure 1). Two-year VA results were similar to the 1-year results, with fewer injections (median of 2-4 ranibizumab injections or 1 triamcinolone injection) required in the second year. Reductions in mean central retinal thickness on OCT were similar in the triamcinolone plus prompt laser group to the 2 ranibizumab groups and greater than in the sham plus prompt laser group. Overall, there was a greater proportion of eyes with a substantial improvement of ≥10 letters and ≥15 letters and a lower proportion of eyes with a substantial worsening of ≥10 letters and ≥15 letters in the 2 ranibizumab groups compared with the sham plus prompt laser group. Furthermore, as shown in Figures 1 and 2, most of the overall improvement in mean VA

Figure 1: DRCR.net Study: Mean change in visual acuity at follow-up visits demonstrating superior visual acuity outcomes in the 2 ranibizumab groups



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and proportion with ≥10 letter improvement from baseline within the ranibizumab-treated groups occurred by the 8-week study visit, with continued improvement through the 1-year primary outcome visit and stabilization thereafter.

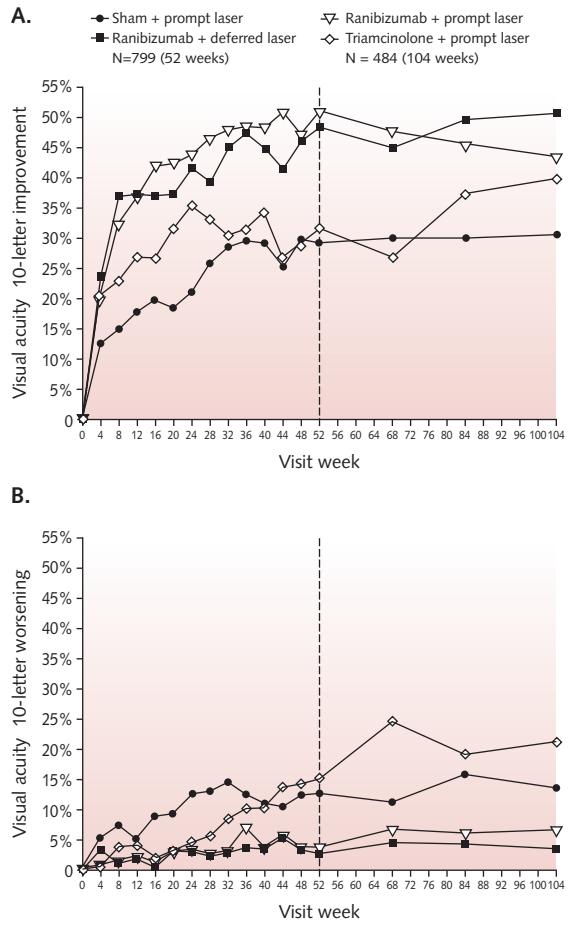
Interestingly, in a subgroup analysis,[11] pseudophakic patients in the triamcinolone group had VA gains similar to patients in the 2 ranibizumab groups. Nonetheless, overall, patients in the 4-mg triamcinolone group had higher incidence of cataracts and raised intraocular pressure.

The median number of injections before the 1-year primary outcome visit was 8 in the ranibizumab plus prompt laser group, 9 in the ranibizumab plus deferred laser group and 3 in the triamcinolone plus prompt laser group.

No systemic safety issues attributable to study treatment were apparent. In particular, there was no increase in the rate of cardiovascular or cerebrovascular events in the ranibizumab groups compared with the other groups. This study, however, was not designed to address safety issues and the sample size was too small to come to a definite conclusion about the safety of repeated ranibizumab injections in diabetic patients in the long-term.

The DRCR.net study makes a strong argument in favour of ranibizumab plus either prompt or deferred laser in the management of centre-involving DME. Although pseudophakic patients seemed to have similar results with IVT to the patients in the ranibizumab arms, there was a higher risk of complications with IVT overall. It is conceivable that some of these complications could have been avoided with similar efficacy had a lower dose of IVT been used in

Figure 2: DRCR.net Study: ≥10 letter improvement (A) and ≥10 letter loss (B) in visual acuity at follow-up visits in the 4 groups



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the study, as has been the case with IVT use in the management of central retinal vein occlusions.[16]

RESOLVE, RESTORE, and READ-2 studies

Further evidence of the efficacy of ranibizumab in fovea-involving DME comes from the RESOLVE (A Randomized, Double-Masked, Multicenter, Phase 2 Study Assessing the Safety and Efficacy of Two Concentrations of Ranibizumab [Intravitreal Injections] Compared With Non-Treatment Control for the Treatment of Diabetic Macular Edema With Center Involvement) and more recently published RESTORE (A Randomized, Double-Masked, Multicenter, Laser-Controlled Phase 3 Study Assessing the Efficacy and Safety of Ranibizumab [Intravitreal Injections] as Adjunctive and Mono-Therapy in Patients With Visual Impairment Due to Diabetic Macular Edema) and READ-2 (Ranibizumab for Edema of the Macula in Diabetes) studies.

The RESOLVE[17] study is a Phase II randomized controlled trial, which demonstrated that ranibizumab monotherapy was well tolerated and significantly more effective than sham injections (with rescue laser) in providing rapid and continuous improvements in best-corrected VA (BCVA) over 12 months (+10.3 letters for ranibizumab vs -1.4 letters for sham; $P<0.0001$).

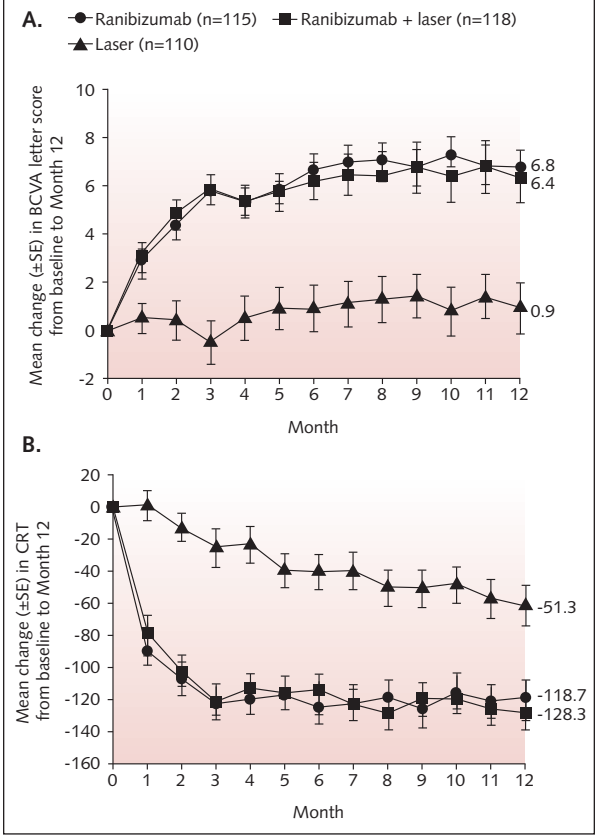
The RESTORE[18] study is a 12-month randomized Phase III study with 345 patients with centre-involving DME with Snellen equivalent VA of 20/32 to 20/160. Patients were randomized to ranibizumab 0.5 mg plus sham laser, ranibizumab 0.5 mg plus laser, or sham injections plus laser. Patients in the ranibizumab plus sham laser arm were given monthly ranibizumab for 3 months followed by as-needed (PRN) dosing based on a detailed retreatment algorithm. Patients in the sham injection/laser arm received laser at baseline followed by PRN laser treatments. The primary outcome measure was the mean average change in BCVA letter score from baseline to month 1 through 12, and safety was also evaluated.

Ranibizumab alone and in combination with laser were found to be superior to laser monotherapy in improving mean average change in BCVA (+6.1 and +5.9 vs 0.8, respectively; both $P<0.0001$). Of note, there was no statistically significant difference detected between the 2 ranibizumab treatment arms ($P=0.61$). Similarly, the mean change ± SD in BCVA letter score from baseline to month 12 was 6.8 ± 8.3 ($P<0.0001$) in the ranibizumab arm, 6.4 ± 11.8 ($P=0.0004$) in the ranibizumab plus laser arm, and 0.9 ± 11.4 in the laser arm (Figure 3). In both ranibizumab arms, there was a significant improvement in BCVA at month 1 with continued improvement up to month 3 with a sustained improvement to month 12. In the laser arm, mean BCVA stabilized around baseline level and reached a 0.9 letter gain at month 12.

Both ranibizumab groups were also superior in terms of BCVA letter score gain of ≥5, ≥10, and ≥15 letters and proportion of patients with BCVA 20/40 Snellen equivalent compared to baseline, improvements in OCT retinal thickness, resolution of leakage on intravenous fluorescein angiography (IVFA) and health-related quality of life (HRQoL) as measured with the National Eye Institute's 25-item Visual Function Questionnaire. Importantly, RESTORE included a ranibizumab monotherapy arm and it was the first study to include HRQoL outcomes. It also included IVFA at baseline, month 6 and month 12.

The retreatment criteria as of month 3 required that monthly injections continued if stable VA was not reached. Treatment was suspended if a) in the investigator's opinion there was no further BCVA

Figure 3: RESTORE Study: ≥10 letter improvement (A) and ≥10 letter loss (B) in visual acuity at follow-up visits in the 4 groups



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improvement attributable to treatment with intravitreal injections at the last 2 consecutive visits, or b) BCVA letter score ≥84 (approximate Snellen equivalent of 20/20) was observed at the last 2 consecutive visits. Injections in these cases would be reinitiated if there was a decrease in BCVA due to DME progression, confirmed by clinical and/or OCT evaluation or other anatomical and clinical assessments, in the opinion of the investigator. Patients were retreated at monthly intervals until stable VA was reached again. Thus, reinitiation of intravitreal injections encompassed ≥2 successive monthly treatments. Laser retreatments were given in accordance with ETDRS guidelines at intervals no shorter than 3 months from the previous treatment if deemed necessary by the evaluating investigator.

The mean numbers of ranibizumab or sham injections were similar in all 3 groups. After the loading phase of 3 months, patients in the ranibizumab arm received on average 4.1 injections, 3.8 injections in the ranibizumab plus laser arm, and 4.5 sham injections in the laser treated arm. A greater proportion of patients in the ranibizumab arms compared to the laser arm achieved a treatment-free period due to disease improvement.

There were no cases of endophthalmitis in the RESTORE study. There was no increase in risk of cardiovascular or cerebrovascular adverse events (AEs) in the ranibizumab arms.

In summary, the RESTORE study demonstrated that patients treated with ranibizumab alone or in combination with laser treatment achieved superior VA and anatomic (IVFA leakage and OCT central retinal thickness) results compared to patients receiving laser treatment alone. The superiority of ranibizumab was also maintained in all subgroups of DME, including patients with focal or diffuse DME. Ranibizumab treatment did not negatively influence the VA outcome or the progression of macular ischemia, as confirmed by assessing the BCVA at month 12 in the subgroups with or without the presence of ischemia at baseline on IVFA, as well as by the degree of capillary loss in the central subfield from baseline to month 12. It is important to note that RESTORE utilized a PRN retreatment protocol that seemed to maintain the VA gained after the loading phase of 3 ranibizumab injections. However, we do not yet know whether monthly ranibizumab would provide better results. Ongoing ranibizumab clinical trials such as the Ranibizumab Injection in Subjects with clinically significant macular Edema with centre involvement secondary to diabetes mellitus (RISE study)[19] and the Ranibizumab Injection in subjects with clinically significant macular Edema in Diabetes mellitus (RIDE study),[20] where monthly injection of ranibizumab will be given for 24 months, will provide data on maximal VA gains in DME with monthly treatments.

The READ-2 study[21,22] was a smaller study comparing ranibizumab monotherapy, laser monotherapy or combination therapy. The mean improvements in BCVA for the ranibizumab only, combined, and laser-only groups were about 7, 0.5, and 4 letters at the 6-month primary endpoint, respectively, compared with 8, 5, and 7 letters at the month 24 endpoint.

Despite the positive results of these ranibizumab studies, there is reason for caution. Firstly, repeated intravitreal injections increase the risk of a given patient eventually developing endophthalmitis or other ocular complications. Three patients (0.8%) in the ranibizumab arms of the DRCR.net study, the largest of the 3 trials, developed endophthalmitis. Furthermore, 1 patient in the ranibizumab + deferred laser group experienced a progression of their tractional retinal detachment.

Secondly, patients with DME are often in a younger age group compared to patients with age-related macular degeneration (AMD). Repeated injections in this group will be a significant financial

burden for the patient and society, as patients often need to take time off work for their injections. It was encouraging, however, that in the DRCR.net study there were only an average of 2-4 injections in the second year. This allows us to indicate to our patients that, although they will likely require repeated injections, more so in the first year, the requirement for repeated injections appears to be reduced over time.

Thirdly, although no systemic side effects were apparent in any of these studies, this does not guarantee that ranibizumab is safe in diabetics (who are already known to be at increased risk of cerebrovascular or cardiovascular events compared to age-matched controls). The small increased risk of fatal or nonfatal systemic AEs cannot be ruled out, as these studies cannot reasonably be powered to detect such differences. As has been underlined in the infrequent cases of medications that were later found to be associated with increased risk of rare cardiovascular side effects, it will take observational data over years of experience to ensure that there is no significantly increased risk of rare adverse events with intravitreal ranibizumab. Use of this medication in patients with a recent history of stroke, unstable angina, or myocardial infarction requires careful evaluation, including consultation with the patient's other healthcare providers, to determine whether the benefits outweigh the potential risk.

Fourthly, the risk of diabetic macular ischemia with prolonged (over many years) use of intravitreal ranibizumab therapy is unknown. As IVFA was not a part of the DRCR.net protocol, it was impossible to determine the effects of repeated intravitreal ranibizumab on macular perfusion in this study. Of note, however, was that very few patients in the ranibizumab arms lost ≥10 letters of vision, suggesting that this complication is rare, and even if present, does not outweigh the benefits of treatment over 2 years. Furthermore, in the RESTORE study, where IVFA was included in the protocol, there was no evidence of worsening macular ischemia over 1 year of treatment.

Finally, although these studies provide evidence of efficacy in subjects enrolled in the ranibizumab arms, the true effectiveness of the drug may differ in "real life" situations. Although the principles of the retreatment algorithms are relatively straightforward and allow for a deferral of injections, the complexity of these algorithms increases the potential for variations in individual patient response to ranibizumab therapy and a potential loss of effectiveness. These retreatment protocols also required frequent follow-up visits throughout the 2 years, although it is encouraging that in the second year of the DRCR.net study, patients in the ranibizumab arms could have their visits spaced out to 8 and then 16 weeks.

Despite the potential issues and unanswered questions, there is still overwhelming evidence suggesting a benefit of intravitreal ranibizumab alone or in combination with laser in the treatment of fovea-involving DME.

Review of Recent Randomized Clinical Trials for Bevacizumab in DME

Bevacizumab is the full-length humanized monoclonal antibody that binds to all active isoforms of VEGF-A. It remains off-label for use in the eye and there are significantly less data in the literature in relation to its safety and efficacy in various retinal disorders. Despite this, bevacizumab is the most widely used drug for the treatment of neovascular AMD in the United States (US) because of its lower cost than ranibizumab (approximately 1/40th).[23]

The results of the Comparison of Age-related macular degeneration Treatments Trials (CATT)[24] revealed that monthly bevacizumab was non-inferior to monthly ranibizumab in terms of VA gain in the treatment of exudative AMD. Rates of death, myocardial infarction, and stroke were similar for patients receiving ranibizumab or bevacizumab; however, a higher proportion of patients in the bevacizumab arm experienced serious systemic AEs (primarily hospitalizations) than with ranibizumab (24.1% vs 19.0%; risk ratio, 1.29, 95% confidence interval, 1.01 to 1.66). It should be pointed out that the additional serious systemic AEs in the bevacizumab group were broadly distributed in disease categories that have not previously been identified as areas of concern, even in patients who received systemic intravenous bevacizumab, and therefore further study and follow-up will be required to determine if this increased risk is more than a chance occurrence. Although CATT was not powered (as with all clinical trials involving ranibizumab) to determine the safety of the drug in relation to rare systemic AEs, it nonetheless provides some guidance as to the relative efficacy and safety of the 2 drugs in AMD.

Intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema (BOLT Study)

The BOLT study[25] was a prospective single-centre randomized trial of 80 eyes of 80 patients with fovea-involving clinically signficant macular edema and at least 1 prior macular laser treatment (MLT). Patients were randomized to intravitreal bevacizumab every 6 weeks (minimum 3 injections and maximum 9 injections in the first 12 months) or MLT every 4 months (minimum of 1 treatment and maximum of 4 treatments in the first 12 months). The primary endpoint was the difference in BCVA at 12 months between the bevacizumab and laser arms. From baseline to 12 months, patients in the bevacizumab group gained a median of 8 ETDRS letters, whereas

the laser group lost a median of 0.5 ETDRS letters (P=0.0002) with corresponding declines in central macular thickness on OCT. The median number of injections was 9 in the bevacizumab group, and the median number of laser treatments was 3 in the MLT group. Bevacizumab was found to be safe with no deaths, thromboembolic events or electrocardiographic changes in the bevacizumab group.

Review of Recent Randomized Clinical Trials for Aflibercept in DME

Aflibercept (VEGF Trap-Eye) is a fully human, soluble, VEGF receptor fusion protein that binds all forms of VEGF-A, along with the related placental growth factor. Aflibercept may potentially allow for a similar VA gain as with other anti-VEGF agents, with potentially fewer injections.

The DA VINCI study

Preliminary results from the DME and VEGF Trap-Eye: Investigation of Clinical Impact (DA VINCI) study were released at the World Ophthalmology Congress in 2010.[26] In this Phase II, double-masked, prospective, randomized, multicentre trial for aflibercept in the treatment of DME, 219 patients with fovea-involving DME were randomized to 5 groups. The control group received MLT at week 1 with repeat laser treatments at 16-week intervals if needed. Two groups received monthly aflibercept 0.5 mg or 2 mg for 6 months. The other 2 groups received 0.5-mg or 2-mg aflibercept monthly for 3 months, followed by either retreatment every 8 weeks or PRN dosing based on specific retreatment criteria. Patients in all 4 aflibercept groups achieved a statistically significant improvement in VA (8.5 to 11.4 letters of vision gained) compared to patients in the laser group (2.5 letters of vision gained) at 24 weeks (P<0.01 for each group versus laser). There were no drug-related systemic AEs reported.

Although the results of the DA VINCI study are promising, we cannot make definite conclusions about the role of aflibercept in the management of DME until the full 1-year results are published and are confirmed by data from a Phase III clinical trial.

Other Treatments for DME

Sustained-delivery steroid implants

In addition to anti-VEGF agents, sustained-delivery steroid implants may have a role in the management of DME. The Long-term Benefit of Sustained-Delivery Fluocinolone Vitreous Inserts for Diabetic Macular Edema (FAME) study[27] assessed the safety and efficacy of intravitreal inserts releasing 0.2 µg/day or 0.5 µg/day of fluocinolone acetonide (FA) in patients with DME. Patients with persistent DME despite at least 1 macular laser treatment were randomized 1:2:2 to sham injection, low-dose insert, or high-dose insert. Patients were eligible for rescue laser at 6 weeks following study drug or sham injection, and retreatment could be given after 1 year.

The primary outcome measure was the percentage of patients with improvement from baseline of BCVA in ETDRS letter score of ≥15 at month 24. The percentage of patients achieving this outcome at 24 months was 28.7% and 28.6% in the low- and high-dose insert groups, respectively, compared with 16.2% in the sham group (P=0.002 for each). The mean improvement in BCVA letter score between baseline and month 24 was 4.4 and 5.4 in the low- and high-dose groups, respectively, compared with 1.7 in the sham group (P=0.02 and P=0.016). Patients in the insert groups, however, required significantly more cataract surgery and incisional glaucoma surgery.

The other potential sustained delivery implant is the dexamethasone drug delivery system, a biodegradable intravitreal implant to provide sustained delivery of 700 µg of preservative-free dexamethasone. This implant has been approved by Health Canada for the treatment of persistent ME following retinal-vein occlusion[28] as well as to treat noninfectious posterior uveitis in the US and Europe. A recent study by the Ozurdex CHAMPLAIN Study Group[29] assessed the role of the dexamethasone intravitreal implant for the treatment of DME in vitrectomized patients. This was a prospective, open-label, 26-week study of 55 patients with a history of previous pars plana vitrectomy and DME in the study eye. Patients received a single 0.7-mg dexamethasone injection. The primary efficacy outcome measure was the change in central retinal thickness from baseline to 26 weeks as measured with OCT. The researchers noted a statistically significant reduction of central retinal thickness at 8 weeks and 26 weeks. Further studies will be required to elucidate the role of the dexamethasone implant in the management of DME.

Vitrectomy surgery

In addition to anti-VEGF agents and various formulations of steroids, vitrectomy surgery with or without peeling of the internal limiting membrane has also been suggested as a potential treatment, particularly for refractory DME. The Triamcinolone versus Inner-limiting Membrane Peeling in Persistent Diabetic macular Edema (TIME) study is currently underway in Europe.[30] Nevertheless, vitrectomy surgery is currently considered to be a reasonable option in patients with persistent refractory DME with evidence of traction on clinical examination and OCT (Figure 4).

Conclusions

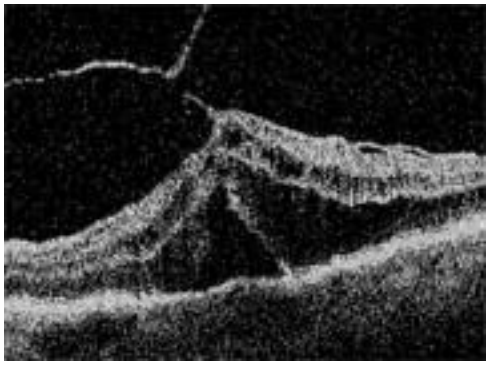
The past few years have seen significant advances in our ability to treat patients with DME, including the resurgence of interest in intravitreal steroids and

the introduction of intravitreal anti-VEGF agents. Despite the evidence reported above, it must be highlighted that, although intravitreal ranibizumab, bevacizumab, and triamcinolone are all routinely used in clinical practice as treatments for DME, only ranibizumab has Health Canada approval for its use in this indication. We also must not forget the proven benefit of good systemic blood sugar and BP control in the management of diabetic retinopathy and DME. There has also been recent evidence from the ACCORD-EYE (The Action of Control Cardiovascular Risk in Diabetes-Eye Study)[31] randomized study of patients with type 2 diabetes demonstrating a significant reduction in the risk of progression of diabetic retinopathy with fenofibrate (a lipid-lowering agent) when added to a statin. Interestingly, there was no benefit of intensive BP control. Furthermore, a recent study demonstrated that early blockade of the renin-angiotensin system with enalapril or losartan reduced the odds of retinopathy progression, independently of changes in BP.[32]

IVT monotherapy has been found to be less effective than MPC as primary treatment for centre-involving DME, and is associated with increased risks of glaucoma and cataracts. However, IVT plus prompt laser achieved similar results to ranibizumab with laser, and better results than laser alone in pseudophakic patients with DME.

Anti-VEGF agents have expanded our armamentarium in the treatment of DME. Several studies have now shown a clear benefit of intravitreal ranibizumab in the short term with no obvious systemic safety issues.

Figure 4: Optical coherence tomography image of a patient with DME and evidence of vitreomacular traction.



Intravitreal bevacizumab given every 6 weeks appears to also be superior to repeated laser in patients with persistent DME despite 1 prior laser treatment. Intravitreal aflibercept appears to be beneficial at 6 months when compared to laser in Phase II studies. Further studies will be required to determine the safety and efficacy of bevacizumab and aflibercept in DME.

It is likely that MPC will continue to play an important role, probably not as primary treatment, but rather as an adjunct to intravitreal therapy in centre-involving DME by hopefully allowing for fewer injections in the long term. MPC remains the standard of care for non-centre-involving clinically significant macular edema.

Sustained-release implants appear to be an effective platform for intraocular steroid delivery. Further

Case Study

A 41-year-old female with type 1 diabetes (diagnosed 10 years ago), hypertension, and hypercholesterolemia presents with a 6-month history of vision loss in both eyes and difficulty driving. She is currently taking metformin, gliclazide, candesartan, amlodipine, atorvastatin, and low-dose acetylsalicylic acid. Her hemoglobin A_{1C} last checked was 7.1%. BCVA was 20/50 OD and 20/80 OS. Anterior segment examination revealed mild nuclear sclerosis in both eyes with normal intraocular pressures. Dilated fundus examination revealed severe nonproliferative diabetic retinopathy in both eyes with centre-involving DME (Figure 5A).

The patient was asked to follow-up with her family doctor to ensure that blood sugar, blood pressure, and cholesterol levels were optimized. After discussing the risks and benefits, the decision was made to proceed with intravitreal ranibizumab in both eyes (right and left eyes treated on separate visits). She was treated with monthly injections for 3 months with significant improvement in DME and improvement in BCVA to 20/25 (right) and 20/30 (left) (Figure 5B).

The patient subsequently experienced a recurrence of edema, and response to further intravitreal ranibizumab injections with maintenance of improved vision. Fluorescein angiography was performed and focal laser carried out in both eyes, and the patient was followed monthly with ranibizumab administed on an as-needed basis according to the DRCR.net retreatment criteria. Improved vision and normal thickness on optical coherence tomography were both maintained.

Figure 5A

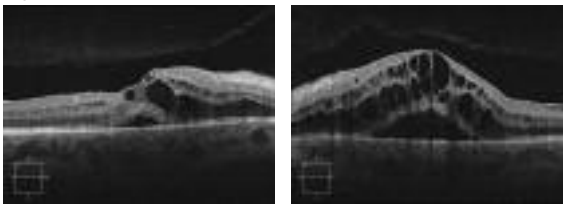
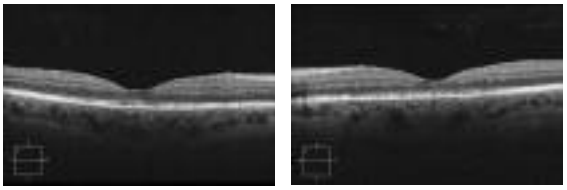


Figure 5B



development of these implants to allow for the slow release of other therapeutic agents, such as anti-VEGF agents, will likely allow for a more manageable treatment paradigm in the coming years.

Dr. Muni is Assistant Professor, Department of Ophthalmology and Vision Sciences, University of Toronto, and Vitreo-Retinal Service, St. Michael's Hospital and The Hospital for Sick Children, Toronto, Ontario. Dr. Kohly is Assistant Professor, Department of Ophthalmology and Vision Sciences, University of Toronto, and Medical Retina Specialist, Sunnybrook Health Sciences Centre, Toronto, Ontario.

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