

Treatment for Diabetic Macular Edema in Japan

BY TOSHINORI MURATA, MD, PhD

The International Diabetes Federation estimates that by the year 2030, 552 million individuals worldwide will have diabetes.¹ Proliferative diabetic retinopathy is the most common cause of severe vision loss in patients with diabetes, but diabetic macular edema (DME) is the most frequent cause of blindness. The prevalence of DME among patients with type 2 diabetes is 14%,² and the 10-year incidence of DME among patients with type 2 diabetes is 25.4%.³ Thus, investigation to find improved treatment modalities for DME has significant value. This article details the current status of DME treatment in Japan.

VITRECTOMY VS FOCAL/GRID LASER

What makes the treatment of DME in Japan unique is the frequent use of vitrectomy: Only a limited number of ophthalmologists including myself perform the global gold standard: ie, focal/grid laser. Although there has been no adequately powered prospective clinical trial comparing the efficacy of vitrectomy and focal/grid laser for resolving DME, most Japanese ophthalmologists judged that vitrectomy works better than focal/grid laser based on their own experiences. Consequently, in the 1990s, vitrectomy prevailed over focal/grid laser in Japan.⁴

VITRECTOMY FOR DME WITHOUT MACULAR TRACTION

It has been widely accepted that vitrectomy is effective in resolving fovea-involving diffuse DME only when it is associated with apparent vitreomacular traction with taut posterior hyaloid.⁵⁻⁷ However, many studies, mainly in Germany,⁸⁻¹¹ Japan,^{4,12-15} and Korea,¹⁶ have reported excellent results regarding DME resolution after vitrectomy even without apparent vitreomacular traction. Unfortunately, these studies are mostly small case series and not randomized trials pitting vitrectomy

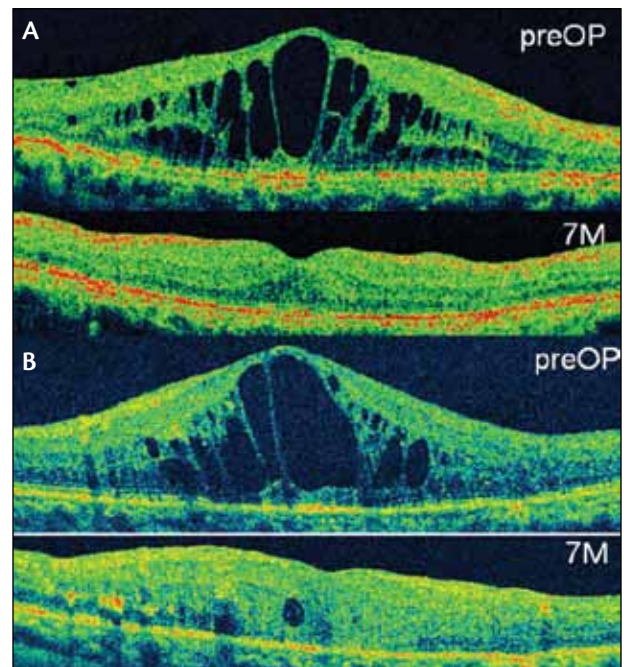


Figure 1. Preoperative cross-sectional optical coherence tomography (OCT) images of 2 different eyes with diffuse DME involving the fovea, with disrupted IS/OS and ELM lines. In the first case, as DME resolved, the IS/OS and ELM lines partially regenerated with vision recovery to 20/20 at 4 months after vitrectomy (A). In the second case, the IS/OS and ELM lines did not regenerate, and vision remained 20/200 at 7 months after vitrectomy. These findings suggest a permanent loss of photoreceptor integrity due to long-lasting DME (B).

against focal/grid laser. In addition, some papers reported a lack of correlation between resolution of DME and vision recovery after vitrectomy.^{9,10,17} Admitting this lack of correlation in some cases, Japanese ophthalmologists still believe vitrectomy is effective in the treatment of fovea-involving diffuse DME.

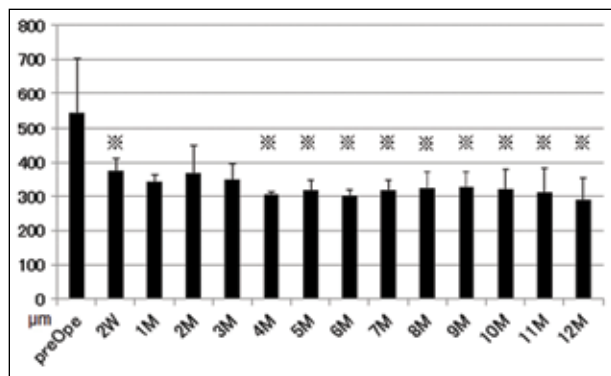


Figure 2. Central macular thickness (CMT) after vitrectomy for DME with ILM peeling. The average CMT decreased significantly at 2 weeks, then rebounded briefly, and decreased again at 4 months and thereafter to 12 months. * = Significant decrease from preoperative CMT.

PHOTORECEPTOR INTEGRITY AND VISION IMPROVEMENT

DME resolution and photoreceptor integrity are both necessary for vision recovery in eyes with DME.¹⁸ Because it is well known that increase in central macular thickness (CMT) due to DME is directly associated with vision deterioration, it has generally been believed that reduction in CMT should lead to improvement in vision. However, subsequent resolution of DME after vitrectomy does not necessarily lead to visual recovery. This paradox may be explained by photoreceptor damage due to prolonged DME involving the fovea, which may be seen as a loss of integrity of the photoreceptor inner segment/outer segment (IS/OS) or the external limiting membrane (ELM) line (Figure 1).^{8,11,12,18}

DME RESOLUTION WITH VITRECTOMY

In a study we conducted, triamcinolone-assisted vitrectomy with internal limiting membrane (ILM) peeling provided prompt (in 2 weeks) resolution of DME, which is critical to evade photoreceptor damage due to long-lasting DME. Triamcinolone was used for intraoperative visualization of the posterior hyaloid. Because the effect of intraoperative triamcinolone decreases with time, this may have allowed the DME to rebound mildly before decreasing significantly again at 4 months and remaining stable throughout the study period (Figure 2). Once resolution of DME is obtained after vitrectomy, the effect is long-lasting. The study with the longest reported follow-up, up to 170 months (mean of 74 months), suggested no recurrence of DME.¹⁴

However, 1 major drawback of vitrectomy is the significantly decreased retention time of anti-VEGF drugs postoperatively.¹⁹ If DME persists after vitrectomy, more

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injections of anti-VEGF drugs are required. Clinical findings that predict persistent DME after vitrectomy have yet to be elucidated.

PROMPT BUT TRANSIENT RESOLUTION WITH ANTI-VEGF DRUGS

Prospective clinical trials evaluating the effect of repeated intravitreal injection of anti-VEGF drugs in the treatment of DME, including READ-2, RESOLVE, RESTORE, RISE and RIDE, DRCR.net protocol, BOLT, and DA VINCI, have demonstrated significantly improved visual outcomes. In most eyes with DME in these trials, anti-VEGF monotherapy provided prompt resolution of DME, which is critical to evade irreversible damage to photoreceptors, and resultant vision recovery.

DME resolution from focal/grid laser occurs much slower than that from ranibizumab. In the report from the DRCR.net, the reduction of CMT in laser-treated eyes took 1 year to reach a comparable level to that from ranibizumab injections, and unfortunately vision did not recover.²⁰ In the READ-2 study, 1 arm was treated with only focal/grid laser for 6 months, and patients in this arm were then allowed to take intravitreal injections in addition to the focal/grid laser. However, vision recovery was not comparable to that in the arm treated with ranibizumab from the beginning.²¹ These reports suggest that 6-month duration of DME causes irreversible damage to the photoreceptors, and vision does not recover even if DME shows significant resolution.

Anti-VEGF therapy provides prompt resolution of DME, which is crucial to vision recovery, but its effect is transient, and repeated injections are required. On the other hand, focal/grid laser provides long-lasting effects, but the benefit from laser occurs very slowly over the span of 6 months, thus resulting in limited vision recovery.^{20,21}

REPEATED INTRAVITREAL INJECTIONS

Although anti-VEGF drugs provide significant visual recovery in DME, repeated injections are necessary to maintain their effect. Long-term treatment increases the risk of adverse events so that, after 20 to 40 injections, the cumulative risk of endophthalmitis reaches

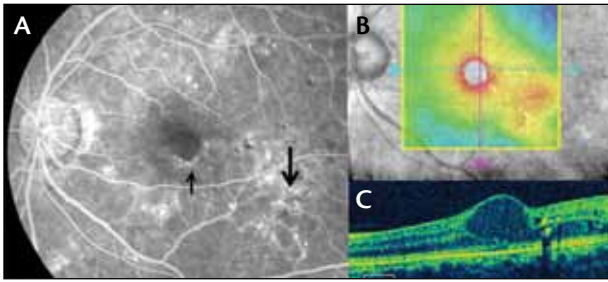


Figure 3. An eye with DME before focal/grid laser. (A) Fluorescein angiography shows perfoveal leakage (small arrow) and nonperfusion area in the macular (large arrow). (B) Retinal thickness map on OCT showing foveal DME (white >500 μm , normal <250 μm). (C) Cross-sectional image on OCT showing foveal DME.

1%.²² In addition, anti-VEGF drugs are very expensive, and expanding health care costs will be called into question. The number of trained ophthalmologists may be insufficient to take care of the increasing number of patients with DME with repeated injections.

VEGF REDUCTION IN DIABETIC RETINA

Anti-VEGF drugs reduce VEGF activity in the retina

by blocking VEGF from binding to VEGF receptors, while laser reduces VEGF synthesis by coagulating VEGF-overexpressing ischemic retina.²³ Figure 3 shows an eye with DME treated with focal/grid laser with panretinal photocoagulation (PRP). DME is known as 1 of the adverse effects of PRP, but extensive PRP can lead to resolution of DME, possibly through decreased intravitreal VEGF synthesis.²⁴ Figure 3 shows foveal DME caused by leakage in the lower perfoveal capillary network. Although focal/grid laser was delivered only to macular nonperfusion areas with PRP, and not directly to the perfoveal leakage, this leakage resolved spontaneously in 7 months (Figure 4). Recently, 3-year outcomes of the READ-2 study reported over-aggressive focal/grid laser reduced the numbers of ranibizumab injections needed to resolve DME, possibly due to this VEGF-lowering effect of laser treatment.

COMBINED THERAPY WITH ANTI-VEGF DRUGS AND LASER

As reported in the READ-2 study, combined therapy with anti-VEGF drugs and focal/grid laser may reduce the need for repeated anti-VEGF injections,²¹ which may otherwise last for years, possibly even indefinitely. To rescue

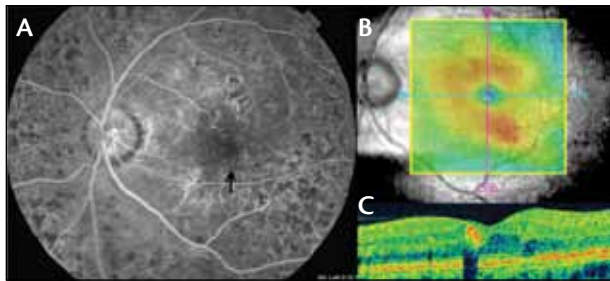


Figure 4. Same eye with DME 7 months after focal/grid laser with panretinal photocoagulation. (A) Fluorescein angiography shows perifoveal leakage resolved without direct laser (small arrow). (B) Retinal thickness map on OCT showing foveal depression (blue <250 μm). (C) Cross-sectional image on OCT showing foveal depression.

Further investigation to determine clinical findings that predict the risk of persistent DME after vitrectomy is necessary.

photoreceptors from DME-related damage, anti-VEGF drugs are essential in the early phase of treatment until focal/grid laser with or without PRP can provide significant VEGF reduction in the retina.

LIMITED ROLE OF INTRAVITREAL STEROIDS

Although intravitreal injections of steroids are as effective as anti-VEGF drugs in resolving DME, these are no longer commonly performed in Japan. Because the risks of secondary cataract and glaucoma are relatively high, steroids may have a limited role to treat DME in pseudophakic steroid nonresponders. On the other hand, sub-Tenon injection of triamcinolone, often associated with direct laser to leaking microaneurysms, is commonly performed, as it has a negligibly low complication risk. Sub-Tenon injection should be equally effective even after vitrectomy.

CONCLUSION

Because many prospective clinical trials evaluating the effect of repeated intravitreal injection of anti-VEGF drugs in the treatment of DME have demonstrated significantly improved visual outcomes, anti-VEGF treatment is likely to become the first line of treatment for DME in Japan. To reduce the need for repeated injections of anti-VEGF drugs, focal/grid laser, PRP, and sub-Tenon injection of triamcinolone will be used.

Vitrectomy should be considered whenever applicable, as it provides both prompt and long-lasting resolution of DME. Further investigation to determine clinical findings that predict the risk of persistent DME after vitrectomy is necessary. We must be ready because ranibizumab will be approved for DME this year in Japan. ■

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