ANTI-VEGF THERAPY FOR DIABETIC MACULAR EDEMA

A roundtable discussion with Franck Fajnkuchen, MD, and Paolo Lanzetta, MD

Case report by Paolo Lanzetta, MD

The answers provided are based on the physician’s own experiences of anti-VEGF treatments in their practices. Labels may vary in other countries and the discussion may not reflect local practice or may not be representative for all patients.
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What is the rationale for the use of anti-VEGF therapy in diabetic macular edema (DME)?

Franck Fajnkuchen, MD: The pathophysiology of DME is not fully understood; nevertheless it is well appreciated that VEGF-A plays a critical role. Specifically, in patients with diabetes, chronic hyperglycemia and when metabolic and vascular changes induce microvascular damage. Those changes, in association with continued inflammation, lead to capillary occlusion and retinal ischemia, leading to an overproduction of VEGF-A. As levels of VEGF A increase, so too does vascular permeability, inducing a breakdown of the inner blood-retinal barrier and leading to macular edema. Because VEGF is involved in DME pathophysiology, and levels of VEGF are increased intraocularly in patients with DME, it makes sense to use targeted therapy that will abate local levels of VEGF.

Paolo Lanzetta, MD: As Dr. Fajnkuchen explained, diabetic retinopathy (DR) is known to increase levels of VEGF in the vitreous. This has been shown in a number of studies in patients with active proliferative DR and DME. VEGF is not only a potent stimulus to vascular proliferation; it is a significant hyperpermeability protein as well. As a result, it is a major cause of blood barrier disruption, leakage, and contributes by several mechanisms to DME.

What is the proper role of anti-VEGF therapy in the management of DME? Is it an appropriate first-line therapy? How does the availability of anti-VEGF agents change the way that patients with DME are treated?

Dr. Fajnkuchen: The availability of anti-VEGF agents has changed the management of patients with DME. The results of the different drugs’ clinical trials seem to agree on one thing: intravitreal injection of anti-VEGF agents provides a functional benefit superior to those observed with photocoagulation in central DME. The visual gain is better, and, perhaps more important, the percentage of patient with a gain of more than 15 letters and a loss of fewer than 15 letters is superior with anti-VEGF compared with laser. It is for these reasons that ranibizumab is currently my first-line therapy choice for patients with central DME.

Treatment with anti-VEGF agents may represent a burden for patients, especially over the first several months when we inject every month. I like to explain to patients that this intensive initial injection regimen contributes to a better visual rehabilitation, and that after the initial phase, the need for reinjection will decrease dramatically. Many of my patients accept this explanation.

Prof. Lanzetta: Currently, we have many options for treating patients with DME. Beside anti-VEGFs, laser is still a valid option in the case of a focal, non–center-involving edema, and subthreshold treatments are becoming more popular. In many cases, I start by drying the retina with drug therapy and subsequently apply laser photocoagulation. Steroids are now available in various formulations, as an intravitreal injection or as a bioerodible or nonerodible implant. Obviously, steroids still carry the risk of increased intraocular pressure or cataract formation, but they may be safer systemically.

Despite the broad therapeutic armamentarium, we should never forget to treat the diabetic patient as a whole individual by recommending strict metabolic control and adequate treatment of hypertension when present.

Dr. Fajnkuchen: I would agree with Professor Lanzetta that the other available therapeutic modalities do have a role. In clinically significant macular edema that is not center-involved, I continue to use photocoagulation as a first line treatment. In central DME, although I start with anti-VEGF injection, I may add laser after 6 months if I observe the persistence of edema arising from microaneurysms. In my practice, I avoid using laser before this delay based on the observations from DRCR.net Protocol I study that an immediate laser may impair the final visual outcome.

Overall, the availability of new therapeutic agents against DME is very positive. Indeed, all patients are not good responders to anti-VEGF, so it is useful to have other therapeutic options such as corticosteroids. However, because of ocular adverse events associated with steroids, notably cataract and intraocular pressure increase, I consider them a second line treatment.
Finally, because DME is a multifactorial pathology, it may be relevant to combine steroids with anti VEGF agents in certain situations. However, there is not enough data to answer this question today.

**Are there differences—in structure, binding properties, or in terms of ocular and systemic pharmacokinetics—among the anti-VEGF agents that are used in DME?**

**Prof. Lanzetta:** There are different anti-VEGF agents currently available, namely, ranibizumab (Lucentis, Novartis), aflibercept (Eylea, Bayer and Regeneron), and bevacizumab (Avastin, Genentech). There are in fact considerable differences among these agents in terms of their molecular structure, binding affinity, and pharmacokinetics: both locally in the eye and systemically. In particular, bevacizumab may have immunogenic effects and it may significantly suppress systemic VEGF levels. The clinical impact of this phenomenon—and in fact the differences in characteristics of these 3 agents—may not be well understood, but this is something we should be aware of when we use these agents in the clinic.

**Dr. Fajnkuchen:** There are other differences between ranibizumab, bevacizumab and aflibercept. They differ in their molecular weight, structure, and pharmacokinetics. It is important to keep in mind that 2 of these agents, ranibizumab and aflibercept, were developed for intracocular injection, and thus why they are on-label treatments.

One important difference in the structure between these 3 molecules is the presence of the Fc fragment. Ranibizumab is a monoclonal antibody fragment, the antigen-binding Fab without the Fc fragment. A recent study by Avery and colleagues concluded that in DME patients, the three VEGF inhibitors (ranibizumab, bevacizumab, and aflibercept) demonstrated different systemic exposures following intravitreal injection. Systemic exposure is highest with bevacizumab followed by aflibercept, presumably due to –Fc recycling by Fc receptors on cells. In addition, free systemic VEGF following 3 doses of intravitreal bevacizumab and aflibercept was substantially lower than with ranibizumab. As Professor Lanzetta correctly pointed out, however, the clinical impact of all these findings are unknown. It would take a very large, well-controlled study to better understand the impact.

**What is the evidence from Level 1 clinical studies supporting the use of anti-VEGF therapy in DME? What can physicians learn from clinical trials for ranibizumab?**

**Prof. Lanzetta:** The RIDE and RISE trials added important data on anti-VEGF treatment of DME, namely that continuous monthly treatment with ranibizumab for 3 years provided unprecedented outcomes, especially when compared with laser therapy.

**Dr. Fajnkuchen:** I agree. RISE and RIDE let us know some very important information that we can take into the clinic. First, that after intravitreal injections, we may observe a prompt functional and anatomical response. Those results were sustained over a 36 month period. Second, with monthly injections, patients were less likely to progress to more advanced DR; in fact, many ranibizumab-treated eyes experienced improvement in DR severity. Third, what is in my opinion a very important point, is that the 36-month results of RISE and RIDE suggest that a 24-month delay in initiation of ranibizumab therapy may result in a certain amount of vision loss that is irreversible. In DME, as opposed to AMD, the classic thinking is that initiation of treatment is not an emergency; nevertheless, it may be deleterious to wait too long before starting treatment.

**How do results with ranibizumab versus sham relate to those from studies of ranibizumab versus laser (eg, DRCR.net Protocol I and RESTORE)?**

**Dr. Fajnkuchen:** The key learning from DRCR.net Protocol I and RESTORE is that visual acuity benefits obtained after the loading phase of treatment are sustained with an as needed, or PRN, regimen. Additionally, combining laser and ranibizumab injections does not provide an additional benefit in terms of visual and anatomic response, and neither does that approach reduce the number of injections. The DRCR.net Protocol I study 3-year results indicated that focal/grid laser treatment at the initiation of intravitreal ranibizumab is no better, and possibly even worse for vision outcomes, than deferring laser treatment for 24 weeks or more in eyes with DME. In my opinion, an important finding from the 36 months results of both of these trials is the change in need for retreatment over time, with patients requiring fewer than 3 injections during the final year.

**Prof. Lanzetta:** Most trials comparing ranibizumab with laser treatment have shown that the 2 therapies together do not provide additional benefit in terms of visual acuity gain or reduced frequency of injection compared with ranibizumab monotherapy. However, we...
need more evidence to conclude that laser in combination with anti-VEGF should not be recommended.

What is the significance of the data from BOLT showing vision gains with bevacizumab?

Prof Lanzetta: The BOLT study shows that bevacizumab may be efficacious and superior to laser photocoagulation in the treatment of DME, but it did not address the safety of bevacizumab when used off-label in the eye.

Dr. Fajnkuchen: In France, due to legal issues and because ranibizumab is reimbursed for use in DME, physicians are not allowed to use bevacizumab to treat DME. Many studies have confirmed the efficacy of bevacizumab in DME patients. However, few studies have directly compared ranibizumab and bevacizumab. In a 48-week study, Nepomuceno et al showed that intravitreal ranibizumab was associated with greater improvement in BCVA at some visits, and the mean number of injections was higher in the intravitreal bevacizumab group. However, those findings were not confirmed by other studies. Moreover, the safety of bevacizumab remains the greatest point of controversy.

What do the results from DAVINCI and VIVID/VISTA add to the discussion?

Dr. Fajnkuchen: Aflibercept was recently approved by the European Medicines Agency for treatment of DME. After 52 weeks, patients in the VIVID/VISTA study receiving a regimen of 2.0 mg aflibercept every 8 weeks after 5 initial doses gained 10.7 letters. Adverse events were typical of those seen in other studies in patients with diabetes receiving intravitreal anti-VEGF therapy.

In my mind, there are 2 questions that need to be answered about using aflibercept in DME: (1) in cases of resistance to one anti-VEGF, is it better to change from 1 anti-VEGF to another (for instance, switch from ranibizumab to aflibercept), or is it better to switch to steroids; and (2) is there a difference in efficacy between 2.0-mg aflibercept, 0.5-mg ranibizumab, and 1.25-mg bevacizumab? A randomized comparative study will be needed to answer the second question. Randomization is needed in order to include comparable patients in different study arms, especially in terms of initial visual acuity between the different groups.

Prof. Lanzetta: The aflibercept trials have supplied the evidence that a second anti-VEGF formulated for ocular use is efficacious in the treatment of not only AMD, but also DME. We need more time to verify whether the outcomes within the registration studies can be applied to clinical practice where patients differ greatly in terms of disease type, baseline visual acuity, and metabolic control.

Are there any ocular and/or systemic safety risks associated with anti-VEGF use?

Dr. Fajnkuchen: We know that a diabetic patient has a higher susceptibility to infections, and thus, it is important to assess if a patient with diabetes mellitus is more prone to postinjection endophthalmitis. With ranibizumab, major trials have shown that the incidence of this complication is not more frequent than in non-diabetic patients.

A recent study suggested that in AMD patients, the risk of endophthalmitis may differ between different drugs and that the risk may be higher following treatment with aflibercept. Kelly and colleagues noted 1 endophthalmitis event for every 945 injections with aflibercept but 1 endophthalmitis case for every 1561 injections of ranibizumab. Is this difference related to structural difference between these two molecules? Might the presence of the Fc fragment in aflibercept trigger an immunologic inflammation reaction? Additional studies will help answer these questions.

Prof. Lanzetta: The fact is that all on-label anti-VEGF drugs have demonstrated safety in clinical trial settings. That is a large part why the 2 agents, ranibizumab and aflibercept, received indications for use in the first place. As Dr. Fajnkuchen alluded to, though, diabetic patients often have comorbidities that may predispose them to potentially severe side effects with the use of anti-VEGF drugs. Moreover, DME is usually a bilateral condition that may require bilateral injection, and, hence, increased VEGF suppression. This suggests to me that we should be very carefully following patients for ocular and systemic complications.

Dr. Fajnkuchen: One other major concern is the potential for increased adverse events associated with systemic VEGF suppression. Dyslipidemia, hypertension, and arterial thromboembolic events are significant comorbid conditions prevalent in people with diabetes. Furthermore, patients with DME are at higher risk of myocardial infarction and cerebrovascular accidents than diabetic patients without DME.

That said, we should keep in mind the potential issues associated with the systemic VEGF suppression and be mindful of systemic adverse that may be related, especially given the recent data from Avery.

With Lucentis’ new EU label and thus the ability now to ‘personalize treatment’ for DME patients and the recent results from the RETAIN study, do you anticipate introducing the treat-and-extend treatment regimen approach in your clinic?

Dr. Fajnkuchen: A treatment schema involving monthly visits is going to be difficult to maintain over
studies showed that the need for injection sharply decreases after an initial period of intensive treatment. Moreover, in the RETAIN study, the majority of patients had an interval of 2 months or more between treatments at 2 years. From this, it would seem that monthly monitoring over a long period seems to be unnecessary for DME patients. The new EU label allows us to treat patients according to the recurrence rates we experience in real life scenarios—and that is to say, they are quite different than what may have been noted in pivotal clinical trials. So, yes, I think the new label can result in improved clinical efficiency, but more importantly, it may help us get improved motivation and compliance from patients if we can tell patients at the onset of treatment that we may be able to eventually reduce their shot burden.

Prof. Lanzetta: I take a more guarded approach to this question. The new label for ranibizumab in the EU introduces more flexibility in the management of our patients and recognizes that the treating physician is an expert on macular diseases with extensive experience in the usage of Lucentis—and, therefore, is best qualified to make decisions about how to treat these patients. But, there are advantages and disadvantages to treat and extend. I agree with the idea that a skilled retina specialist will be able to identify those patients who will get the maximum benefit from a less-than-monthly regimen. However, we must be very careful with how this will play out in real life scenarios. Anecdotal evidence suggests that physicians and patients deviate quite dramatically from any given intended treatment protocol, resulting in suboptimal outcomes. I would propose that the successful use of treat and extend will require physicians to have a strong knowledge of the disease they are treating, how it is manifesting in the individual patient, as well as realistic expectations as to the patient’s compliance with monitoring and therapy visits.

Lastly, the new EU label eliminates the requirement for monthly monitoring for DME patients. Do you believe this will improve your clinic efficiency?

Dr. Fajnkuchen: Data from DRCR.net and RESTORE6-8 studies showed that the need for injection sharply decreases after an initial period of intensive treatment. Moreover, in the RETAIN study, the majority of patients had an interval of 2 months or more between treatments at 2 years. From this, it would seem that monthly monitoring over a long period seems to be unnecessary for DME patients. The new EU label allows us to treat patients according to the recurrence rates we experience in real life scenarios—and that is to say, they are quite different than what may have been noted in pivotal clinical trials. So, yes, I think the new label can result in improved clinical efficiency, but more importantly, it may help us get improved motivation and compliance from patients if we can tell patients at the onset of treatment that we may be able to eventually reduce their shot burden.

Variable Responses to Intravitreal Anti-VEGF Therapy for DME

PAOLO LANZETTA, MD

CASE NO. 1
A 64-year-old woman with diabetes mellitus since 2002 presented to our clinic. She was on an oral antidiabetic medication at the time of the consultation. Her medical records indicated that she had been diagnosed with diabetic macular edema in January of 2011 and that she had received focal laser 1 year prior to our examination. Her HbA1c level was 7.8%.

Clinical examination revealed a BCVA of 20/32 (75 ETDRS letters) and a central macular thickness (CMT) of 501 µm at baseline (Figure 1). A regimen of 3 monthly intravitreal injections of ranibizumab (Lucentis, Novartis) was initiated.

After 3 injections, BCVA improved to 20/20 (81 ETDRS letters) and CMT decreased to 283 µm (Figure 2). The

Figure 1.

Figure 2.

Figure 3.

Figure 4.

Figure 5.
patient was followed out to month 12 without further injections. At the 12 month visit, BCVA was 20/25 and CMT was stable at 284 µm (Figure 3).

The patient was seen again in our clinic 6 months later, or 18 months since our initial examination. No further intravitreal injections of ranibizumab were given beyond the 3 initial doses. At the 18 month follow up, BCVA was 20/20 (82 ETDRS letters) and CMT was 279 µm (Figure 4).

**CASE NO. 2**

An 80-year-old man with type 2 diabetes mellitus since 2000 presented to our clinic for evaluation of his DME, which was diagnosed in 2006. The patient was on an oral antidiabetic therapy at the time of the examination. His HbA1c level was 9.5%. Medical records indicated previous ocular history of 5 intravitreal steroid injections (triamcinolone acetonide), cataract surgery with IOL implantation 1 year prior, and focal laser 6 months prior.

Clinical examination revealed a BCVA of 20/160 and a CMT of 763 µm at baseline (Figure 5). Treatment was initiated with 6 intravitreal injections of ranibizumab.

After 6 months, the patient’s BCVA was still 20/160 and CMT was 784 µm (Figure 6). Intravitreal injections were continued for an additional 6 months, and at the 12-month visit, BCVA was 20/100 and CMT was 272 µm (Figure 7). Intravitreal injections were again continued out to month 15. After a total of 36 months of follow up, the patient was evaluated again. The BCVA was stable at 20/100 and CMT was 197 µm (Figure 8).

**DISCUSSION**

The two cases here demonstrate that response to anti-VEGF therapy will vary from patient to patient. Whereas the patient in case 1 demonstrated an immediate anatomical and functional response to therapy after just 3 loading doses, the patient in case number 2 required 15 monthly doses before demonstrating a response. Furthermore, in case 1, anti-VEGF therapy was durable, with demonstrated reduction in CMT and improvement in BCVA out to month 18. The patient in case 2 never recovered visual acuity beyond 20/100, likely due to underlying changes to the retina secondary to DME. However, it should be noted that in case 2, there was a durable response to therapy out to month 36 after discontinuation of intravitreal injections at month 15.