

Investigating Treatment Options for Diabetic Macular Edema

BY ARON SHAPIRO WITH MICHAEL TOLENTINO, MD, AND EDWARD QUINLAN, MD

What are some qualifying features that identify patients who will work well in a clinical trial investigating potential treatments for diabetic macular edema (DME)?

Michael Tolentino, MD: The advances in molecular biology, and the fact that we have a more comprehensive understanding of the molecular basis of diabetic retinopathy, have allowed us to develop scientifically valid treatments. Our experience developing molecular treatments for diabetic retinopathy allows only high-probability molecules to reach humans. With this confidence in the science, any patient who meets the criteria of a clinical trial investigating treatments for DME should be enrolled. In terms of qualifying features, there are really 2 components to consider. The first is that being a patient with diabetes, he or she should be in otherwise adequate health. The second is that patients must be fully invested in the clinical trial and understand that they have the opportunity to reap the benefits of new treatment options. If you are considering a patient for a clinical trial and he or she does not care about his or her own health or well being, he or she is most likely not an ideal clinical trial participant.

Edward Quinlan, MD: Because diabetes is a systemic disease, we must look at our patients with DME in this way. Patients may have cardiac disease or renal dysfunction in addition to their ocular disease. The ideal patient for a clinical trial is one who is not manifesting too many advanced problems as a result of his or her disease, and is overall considered fairly healthy.

You will also want to make sure that the patients you are considering for a clinical trial are invested in the process and are able to follow the study procedures. You can get a feel for this by asking general health questions that explore how up-to-date they are on the status of their condition. For instance, do they know their most recent hemoglobin HbA1c value, or are there any concerns regarding their renal function? I also like to inquire whether a patient is seeing his or her primary care doctor or an endocrinologist on a regular basis. Assessing how engaged a patient is with the

management of his or her condition often gives us a good feel for whether we can depend on him or her to follow the study protocol.

How and when do you take patients off a treatment and enroll them into a study? What is the process?

Dr. Tolentino: In patients with DME, we can identify fairly quickly if they are unresponsive to treatment. Typically, if you do not see any difference after an injection of an anti-VEGF agent or another treatment on optical coherence tomography (OCT), then the patient would be a perfect candidate for a new therapy and can be considered for enrollment in a clinical trial. I am also influenced by a patient's access to care: I may direct toward a trial patients who have limited access to treatment or are limited to only laser or off-label treatments due to financial or insurance reasons.

Dr. Quinlan: You are really looking at 2 groups of patients at this point. Patients in the first group are those who are not responding to a treatment, so they may be more motivated to try a new approach to treatment. We have been fortunate with the advent of anti-VEGF therapy to have another treatment option in addition to laser. However, we have found that not all patients respond well to anti-VEGF therapy. If a patient has undergone a series of injections and has persistent DME, I have found it is fairly easy to discuss considering other treatment options with them, and this may include participation in a clinical trial. Patients in the second group are those who may be responding to anti-VEGF therapy, but for whom the frequent injections are an unsustainable burden. These patients are often younger and have busy lives, and the notion of coming in monthly on an indefinite basis can seem daunting. You may approach this type of patient with the opportunity of exploring other treatment options through clinical trials with the hope that one of these newer agents may extend the treatment interval or decrease the number of treatments needed in the future.

What do you say to patients who are not responding to a current treatment but you think may benefit from a clinical trial?

Dr. Tolentino: The conversation starts by being upfront with the patient, and speaking to them in a way that they can understand. I would first speak to the fact that the patient is not responding to a particular therapy, whether it be an intravitreal injection or laser. I would also explain to the patient that although it may sound simple, diabetes is a complex disease. The current therapies being used to treat DME are really addressing only a single avenue of this very complicated disease. Because of the advances in science, we are able to attack other aspects of pathogenesis. The purpose of clinical trials is to address these other aspects and test new medicines in a safe and controlled manner.

Dr. Quinlan: Often when you mention the words “clinical trial” to a patient, the first thing that comes to his or her mind is “Am I going to be a guinea pig?” In fact, a patient asked me this question just the other day. I like to begin this conversation by informing them that most of the medications they have been using for years to treat other diseases have been subjected to the rigorous clinical trial process to achieve US Food and Drug Administration approval. Patients are often unaware of the approval process the medications they are taking have gone through, and when you explain this process to them, they become more open to participating in a clinical trial. It really starts with giving them an overview of the clinical trial process and highlighting the rigorous nature of pharmacotherapy approval. Highlighting the safety aspects of the study also helps put patients at ease. I explain to them that, during the entire process, we will be monitoring them very closely to ensure their safety. We will be watching them for any signs of an adverse event related to the medication and whether their condition may be worsening or progressing. I also like to mention that entering a clinical trial may actually give them access to a very effective medication in a controlled, standardized, and safe setting before it becomes available to the general public. We have been fortunate to have seen this occur in a number of the clinical trials in which we have participated.

What types of questions do patients usually ask after this discussion?

Dr. Tolentino: Patients often ask why a particular drug does not work. Again, I reiterate to them the complex nature of their disease. Not everyone responds effectively to each therapy option. As a researcher in the 1990s, I helped develop treatments that we now have available, and I am currently helping to develop the next generation of treatments. Some of these medicines address the same target using a better strategy. Others are what we call adjunctive or synergistic to the mechanism of action of the therapies

we are currently using. I always like to ask my patients, “If you are going to knock someone out, do you use just a jab or a combination of punches?” They often respond with, “Well, you would use a jab and an uppercut, or a triple combination, or I would develop a better knockout uppercut.” They understand this analogy and can see that it may take a combination of treatments in order to address the different mechanisms behind their disease. Patients also understand that there are always ways to build better drugs even if they address the same target.

Dr. Quinlan: I am most frequently asked about the safety of the clinical trial. Patients want to be sure that there is not going to be any risk to them. I think it is important to explain the entire clinical trial process. I inform them that medications are initially tested for safety and, once they are shown to be safe and perhaps have shown some efficacy, follow-up studies are conducted to further explore the true efficacy of the treatment. We also provide our patients with an informed consent form, which nicely outlines the trial, including the trial’s goals, how the trial will be conducted, and the known risks associated with the medication. Frequently, patients will read this and comment on the high number of risks associated with a particular medication, but what they do not realize is that many of the other medications they are already taking also come with their own risks. Informed consent provides me with an opportunity to discuss the risks of the medication with the patient and the safety precautions in place. This initial discussion is always the most challenging. I have found that many of our patients who have gone through a clinical trial have enjoyed the experience and are often interested in knowing whether they can participate in another clinical trial. The more they understand the process, the more apt they are to pursue a clinical trial.

What are the biggest challenges for clinical trials investigating treatments for DME?

Dr. Tolentino: The biggest hurdle for clinical trials investigating treatments for DME is that clinicians are more willing to use a drug like bevacizumab (Avastin, Genentech) that has not been evaluated for safety, particularly in patients with diabetes, over enrolling patients in a clinical trial. My patients’ safety is my primary concern, and I actually feel that it is safer to put a patient in a clinical trial than to inject them with something that has not been formally evaluated for safety and toxicity in the diabetic patient population. The reason that we have clinical trials in the first place is so that we do not harm our patients.

Dr. Quinlan: Finding patients who are able to adhere to the clinical trial schedule is one of the biggest challenges in clinical trials investigating treatments for DME. If we

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compare the population of patients with DME to the population of patients with age-related macular degeneration (AMD), we find that we have 2 very different groups. Patients with DME are often young, working, and have busy lifestyles. In contrast, patients with AMD are often older, retired, and have greater flexibility in their schedules. Trials that require monthly visits for 1 or 2 years can be daunting to the younger population of DME patients. Prior to enrollment, it is also important to sit down and have an in-depth discussion with the patient to see if participation in a clinical trial is a good fit. Some considerations include the baseline status, how the patient is responding to treatment, and whether he or she will be able to adhere to the confines of the clinical trial.

What is next for DME research?

Dr. Tolentino: The next generation of drugs that are coming out at this stage fulfill the hypothesis that we had back in the 1990s when we were working on all these molecules in the laboratory. We are finding that a lot of these treatments work synergistically with an anti-VEGF strategy because they target DME from multiple directions.

Dr. Quinlan: I believe we are going to see a considerable amount of progress in the way we treat patients with DME. For many years, we were limited to laser therapy or surgery to treat DME and its effects. Laser therapy certainly is an effective treatment; however, it has its limitations and is also a destructive treatment. Surgery carries risks inherent with any invasive procedure. The movement into pharmacotherapy is much welcomed, and the introduction of anti-VEGF and steroid agents has truly revolutionized our ability to treat our patients. I am hopeful that as we look at more targets along the pathogenesis pathway we will further expand treatment options for our DME patients. If the current trend of rising rates of diabetes continues in the United States, there will be a significant need for additional treatments in the future. ■

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