

Clinical Trials in the Anti-VEGF Era

BY ARON SHAPIRO, PETER L. SONKIN, MD, ROBERT E. LEONARD II, MD

The efficacy of the intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents ranibizumab (Lucentis, Genentech) and bevacizumab (Avastin, Genentech) has revolutionized the treatment of wet age-related macular degeneration (AMD). Historically, treatments for wet AMD, such as macular photocoagulation, verteporfin photodynamic therapy (Visudyne PDT, QLT), and pegaptanib sodium (Macugen, Eyetech), the first intravitreal anti-VEGF therapy to be approved, were only able to slow the rate of vision loss in a subset of wet AMD patients.^{1,2} It was not until the development of ranibizumab, a humanized anti-VEGF monoclonal antibody fragment, that vision could be restored to wet AMD patients.³ At the same time, ophthalmologists discovered that bevacizumab, a humanized antibody derived from the same anti-VEGF monoclonal antibody as ranibizumab, seemed to provide a similar treatment benefit to wet AMD patients at a fraction of the cost.⁴ With the possible upcoming approval of aflibercept (Eylea, Regeneron), a soluble fusion protein containing multiple VEGF binding domains, retina specialists will have an armamentarium of three effective anti-VEGF agents for treating wet AMD.⁵ More recently, the considerable value of anti-VEGF therapy has been extended beyond wet AMD. Ranibizumab has been approved for treatment of macular edema following retinal vein occlusion (RVO), and several recent studies have shown that ranibizumab is superior to the current standard of care for diabetic macular edema (DME), with approvals for ranibizumab and aflibercept anticipated.⁶⁻⁸

These available treatment options highlight the tremendous shift regarding the effectiveness of treatments for wet AMD and for off-label use for DME. That being said, it is fair to suggest that the bar for future treatments has been raised. With this, however, comes the inherent difficulty associated with recruiting patients for clinical trials for a disease with which there are already approved treatment options.

Said Dr. Peter Sonkin, MD, one of this article's co-authors, "Now that we have a much better treatment outcome for wet AMD patients, it does present two

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new challenges in recruiting efforts for clinical trials: (1) Why would a patient want to be in a clinical trial when we have very good treatments available? and (2) What type of study design is necessary to minimize the risk of a bad or inferior outcome?"

In reality, the decision may often be contingent upon whether the clinical trial is an additive study, combining a therapy with anti-VEGF and potentially reducing the number of injections without compromising the patient's clinical outcome, or simply assessing another novel anti-VEGF therapy. The former may be more appealing to both patients and physicians, as it is something not currently available. As we progress in the anti-VEGF era, we also must be aware of the moral and ethical decisions with regard to both recruiting patients and patients' well-being throughout the duration of any clinical trial.

UNMET NEEDS

Despite the obvious benefits of anti-VEGF therapy, there is still a significant unmet need for better treatments for wet AMD and DME. The treatment burden on patients as well as physicians and their practices is high because intravitreal anti-VEGF agents must be administered frequently (often monthly) for patients to maintain the visual benefits. An intravitreal injection is an invasive procedure that can be associated with visually threatening side effects such as endophthalmitis.⁹ Although the absolute risk is low, it increases in proportion to the number of injections administered to the patient. In addition, the need for monthly visits to the ophthalmologist can be onerous and burdensome, and failure to maintain appropriate follow-up leaves patients prone to potentially irreversible loss of vision.

Due to these limitations, there are a number of potential new therapies for wet AMD and DME in clinical development, which means that there is an ongoing need to design and manage clinical trials and to recruit patients. In this context, the availability of effective therapies, such as ranibizumab, has made study design and patient recruitment more challenging; consequently, physicians are also challenged to decide whether a patient is both physically and mentally able to enter into a clinical trial or is better off simply receiving treatment.

PATIENT RECRUITMENT

When recruiting patients to participate in any clinical trial, the investigator must explain the risks and potential benefits of study participation to the patient. In addition, the physician must review the treatment options available to the patient if he or she declines to participate.

Another co-author of this article, Robert E. Leonard II, MD, said, "I think one of the key things in terms of recruiting for clinical research is to find out what kind of patients are going to be good candidates for a particular trial. We always look at the eye criteria, but it is also important to look at the patient's overall health. It is important to ask 'Will this be a patient who is going to be able to complete a clinical trial?' Much of this process has to do with the attitude of the patient. Every patient has his or her own level of comfort with the potential risk of a clinical trial."

Additionally, Dr. Sonkin believes that enthusiasm among the physicians who will serve as the principal investigators of the clinical trial is imperative to successful recruitment. "The more enthusiastic they are about the study, the more effective they and their partners will be at recruiting subjects," he said.

It is not uncommon, however, for physicians to decline to participate in a clinical trial due to concerns about the supporting data or the design of the trial. Before ranibizumab and bevacizumab were available, the best available therapies, such as verteporfin PDT, could at best delay the rate of visual loss and provide a "less worse" visual outcome. As a result, both patients and physicians had strong incentives to participate in clinical trials evaluating therapies that had the potential to provide better visual outcomes to patients.

With the availability of anti-VEGF agents, many wet AMD patients can now expect to maintain or improve their vision with standard-of-care therapy. In addition, wet AMD patients receiving anti-VEGF therapy are significantly less likely to experience a sudden, catastrophic loss of vision due to subretinal hemorrhage. The

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minority of patients who do not respond well to anti-VEGF agents remain interested in participating in trials of novel therapies with the potential to be more effective than current anti-VEGF agents. In addition, patients continue to be interested in treatments that may reduce the burden of frequent intravitreal injections.

"One of the biggest problems facing retinal specialists today is the burden of intravitreal injections," said Dr. Leonard. "As long as you are in practice, you collect patients who require extremely close follow-up, in addition to close injection schedules, which can make clinics difficult to manage. Having fewer injections would benefit both the physician and the patient because we must always remember that intravitreal injections are not without risk. There is a whole host of complications from intravitreal injections, and although fortunately they are low in frequency, they can be very severe. I think reducing injections protects the patients by minimizing the number of injections they receive, in turn potentially limiting risks, and allows the clinician more leeway in already overscheduled clinics.

Several strategies for reducing treatment burden are currently in development, including antiangiogenic gene therapies, adjunctive therapies, and therapies that can be administered less invasively. For example, iCo-007 (iCo Therapeutics, Inc.) is a second-generation antisense inhibitor targeting C-raf kinase messenger RNA (mRNA) for the treatment of retinal neovascular diseases such as diabetic retinopathy and DME.¹⁰ Drug products that prevent the growth of new blood vessels and inhibit increased vascular permeability may have the potential to treat neovascular diseases. However, treatment-naïve patients are more reluctant to enroll in studies in which they may not receive immediate treatment with intravitreal anti-VEGF therapy due to the potential risks of vision loss. This is particularly true in the case of phase 1 studies, when data on safety and efficacy in humans are not available.

The risks and benefits to study participation for patients with DME are somewhat different. Although the current standard of care for DME is focal laser photocoagulation, several recent randomized controlled trials have shown that intravitreal anti-VEGF therapy is superior to laser. Although ranibizumab and aflibercept

have not yet been approved for this indication, future approval of both of these agents is anticipated, and many ophthalmologists consider anti-VEGF therapy to be the de facto standard of care for DME. It is important to note that the characteristic progression of DME is quite different from that of wet AMD. In general, progression of DME tends to be more chronic than wet AMD, with a less immediate threat of irreversible vision loss. As a result, physicians often feel more comfortable allowing some DME patients to defer anti-VEGF therapy in order to participate in a clinical study. However, this depends on the specific characteristics of each patient's disease. In the case of patients whose DME appears to be more chronic, ischemic, and cystic in nature, physicians are far more likely to recommend immediate initiation of anti-VEGF therapy, rather than the deferral of anti-VEGF therapy that would be necessary for clinical study participation.

CONSIDERATIONS IN STUDY DESIGN

In designing a clinical trial for wet AMD or DME, it is critical that appropriate measures are put in place to protect patients' visual health and mitigate the risks associated with participation in the trial, particularly if participation means deferral of an efficacious therapy such as ranibizumab. In masked clinical trials, the safety monitoring committee plays a critical role in identifying patients who may need to exit from the study to receive a nonallowed treatment. Furthermore, principal investigators always have the authority to withdraw a subject from the study in order to provide standard-of-care therapy. It is also typical to allow nonresponding patients access to "rescue therapy" in the event that they experience a decline in vision.

"In all clinical trials, the principal investigator has the option to exit a patient from the study if that patient is not responding to treatment and expresses a disinterest in further involvement," said Dr. Leonard. "If a certain degree of vision loss occurs in a patient in a trial, it is important that there be access to a rescue therapy that will hopefully allow a better outcome."

In the case of wet AMD, rescue therapy is likely to be ranibizumab; in the case of DME, where anti-VEGF agents do not have regulatory approval, rescue therapy is typically focal laser photocoagulation.

Given the proven efficacy of anti-VEGF therapy for wet AMD, it is no longer acceptable for a study to have a sham control. Instead, anti-VEGF therapy must be administered to the control arm, with efficacy of the novel therapy assessed by means of a noninferiority or superiority paradigm. Another acceptable study design would be assessment of an adjunctive therapy to anti-

VEGF agents. In such a study, both active and control arms would receive anti-VEGF therapy, and the active arm would also receive the experimental treatment. The goal of such a study would be to show that administration of the adjunctive therapy with anti-VEGF treatment provides a superior visual outcome to anti-VEGF alone, or that use of the adjunctive therapy provides an equal visual outcome with a clinically meaningful reduction in the number of intravitreal injections required to maintain the visual benefit.

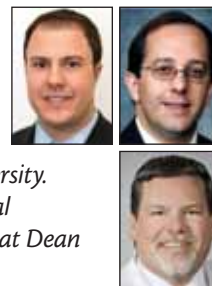
SUMMARY

Despite the remarkable success of intravitreal anti-VEGF therapy in maintaining or improving vision in patients with wet AMD and DME, there is still an unmet need for better, less burdensome, and less invasive treatments. In designing clinical trials for novel treatments for these indications, it is critical that appropriate measures be taken to mitigate risk to patients and ensure that access to anti-VEGF therapy is available when indicated. Furthermore, it is important that physicians evaluate their patients individually in order to make appropriate decisions on a case-by-case basis. ■

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