Translating Clinical Trial Results to Practice

WITH DAVID BOYER, MD; MATTHEW BENZ, MD; AND ALEXANDER EATON, MD

The clinical research process that takes a promising new treatment from initial investigation through US Food and Drug Administration (FDA) approval is arduous and produces a vast amount of clinical data on the safety and efficacy of new therapeutic topics. Interpreting and applying information from clinical trials requires critical evaluation and assimilation, particularly when several sets of data are newly available. This month's column features David S. Boyer, MD; Matthew S. Benz, MD; and Alexander M. Eaton, MD, and their thoughts on how to put clinical trial results into practice.

WHEN SEVERAL SETS OF DATA ARE NEWLY AVAILABLE, WHAT SORT OF DUE DILIGENCE DO YOU TAKE ON TO DECIDE WHETHER A DATA SET IS VALUABLE AND REPRESENTS SOMETHING THAT SHOULD BE APPLIED TO YOUR CLINICAL PRACTICE?

Dr. Eaton: When looking at a data set, the first step in deciding whether it is valuable to your practice is to take a close review of enrollment and patient selection criteria. This is especially important when making comparisons to other studies. Ideally, the enrollment and patient selection criteria would be similar, but in the event that they are not, it is crucial to keep a mental note of any differences so you can take into account any discrepancies when reviewing the results. The second step is to look at the study design. When we are looking at a new medication or treatment, the trial is likely going to be a randomized, masked trial, which may offer a greater sense of confidence in the data. Once you have an established understanding of the trial components, the third step is to look at the top-line numbers. For example, you might closely analyze the differences in the main outcome measure in the study; for wet age-related macular degeneration (AMD) trials, this is typically the letters of improvement. Secondary measures are also of interest and may include the number of retreatments, the length of time between retreatments, and other parameters such as the response of retinal edema and the difference, if any, between the 2 groups. If there is no correlation between vision and retinal edema, I would become more skeptical about the results than if the vision closely tracks improvement in retinal edema. A final point to consider is the emerging global expansion of clinical trials. As trials expand to encompass different geographical regions, it is important to take note of differences in ethnicities. Along those lines, it is in the best interest of your practice to look particularly closely at data that come from your geographic region, because these will more closely parallel what you will encounter. Ultimately, different designs and endpoints make it tricky to directly compare studies, so making a mental note of study differences and keeping those notes at the forefront of your mind will help to put meaning to the data set.

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Dr. Boyer: Whenever a new set of data is being presented, it is important to first look at the inclusion and exclusion criteria. This will set the stage for what kinds of patients were included and how this may afffect your particular practice. To that end, an additional point to consider is how many patients completed the study. If there is a high discontinuation rate, it sends a signal to the physician that there may have been some issues within the study. The size of the study will also play a role in analyzing a new data set. As you begin to digest the data, you will want to determine if the results were statistically significant or just trending toward significant. The physician must then put this into the perspective of his or her own practice to determine clinical significance. Finally, you will want to look at the comparator, whether sham or standard of care. For the AMD noninferiority trials since the introduction of anti-VEGF agents, the comparator is standard of care.

WHAT ARE THE CLINICAL IMPLICATIONS OF APPLYING A PARTICULAR DATA SET TO PRACTICE, AND HOW DO YOU APPROACH APPLYING THESE RESULTS TO YOUR PRACTICE?

Dr. Boyer: The clinical implications of applying a new data set to your practice depend on the frequency with which you treat patients [as opposed to utilizing the treatment regimen employed in a clinical trial]. I tend to utilize a treat-and-extend method, which allows me to gain more information by following the patient carefully. Using this method, you may find that patients require more, or ideally less, treatment. With a treat-and-extend regimen [for wet AMD], I start out by giving my patients 3 loading doses of anti-VEGF therapy, and if they are dry and responding well to treatment, I extend treatment intervals by 1 or 2 weeks, depending on the status of the fellow eye. I do not immediately transition to injections every other month until I see how that patient responds. Seeing how each patient responds is key because there are some patients I call "VEGF-addicts"—patients who require a significant amount of VEGF and do not dry up very easily, thus requiring treatment monthly or even every 2 weeks.

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Dr. Benz: For practices that have had the opportunity to use new drugs coming to market in clinical trials, it may be easier to transition rather quickly if they have experience with a particular drug and have felt comfortable with the drug for a number of years. For clinicians who are less familiar with a drug, it is reasonable to take a more conservative approach and establish some clinical experience before proceeding. To that regard, when transitioning from 1 treatment to another, it may be helpful to do more intensive imaging until the clinician feels comfortable with how the new drug is working and how patients are responding.

Dr. Eaton: Once you have decided to incorporate a new drug into your practice, it is prudent to be cautious, at least initially. There is really no way of knowing how a patient on an older [wet AMD] therapy may respond

when switching to a new therapy. My approach in this setting is to start out with patients who are "incomplete responders"—patients who do not exhibit a full clearing of their retinal edema. One exception to this, however, is patients who have retinal pigment epithelial (RPE) detachments. If a patient presents with an RPE detachment with subretinal fluid but with good vision, I will keep them on their current treatment and refrain from transitioning to a new drug because switching therapy in these patients may increase the risk for RPE tearing.

HOW DO YOU INTERPRET NONINFERIORITY DATA?

Dr. Benz: When interpreting any data set, we must always remember the reason behind trial initiation. When evaluating the results of a noninferiority trial, it is important to consider the treatment arms and what you consider to be truly noninferior. In AMD trials 10 years ago, a successful data set may have been considered to result in a loss of 3 lines of vision, but with the advances in treatment, this is no longer the case. Generally speaking, the primary endpoint in noninferiority trials is visual acuity gains. Other secondary endpoints, however, such as safety and anatomic data, can help in determining whether 1 arm did better than another, and if the data set is relevant to your particular practice.

Dr. Boyer: Only recently have we established [wet AMD] treatments that have proven to be effective, but prior to this, trials could be conducted with either observation or placebo treatment, photodynamic therapy, or some other means of treatment. Now that we have established effective treatments, the only way a new drug is likely to be approved by the FDA is to conduct an noninferiority trial to prove that the new drug is not inferior to the established gold standard. As we move forward, there is no doubt that the industry will see more noninferiority trials rather than placebo-driven trials.

In my opinion, one of the most critical elements of a noninferiority trial is a close examination of statistically significant noninferiority power. Even though data may have reached statistical significance, a 4-letter difference in a large study will catch my eye and will prompt me to pay close attention to whether my patients are experiencing different responses.

HOW DO YOU BALANCE RESULTS FROM CLINICAL TRIALS FOR A GIVEN TREATMENT WITH A PATIENT'S MEDICAL INSURANCE OR HEALTH CARE INSURANCE?

Dr. Eaton: Medical insurance or health care insurance will always play a critical role in patient care. I always outline the different available options for my patients, but ultimately the decision is theirs. In my opinion, it often makes more sense for the majority of patients to select a therapy that does not require as many retreatments, particularly if they have good insurance coverage.

Dr. Boyer: Even with good results from a clinical trial, a new drug coming to market still awaits FDA approval first and foremost, and subsequently Centers for Medicare and Medicaid Services approval. Many times there is a further lag period for health maintenance organizations (HMOs) and even Medicare. Because of this, physicians should be aware that there is a slight risk in reimbursement when starting patients on new drugs, particularly in HMO plans. Many of the new drugs coming to market are fairly costly, and so manufacturers will likely have patient-assistance plans. This is extremely helpful when a patient is slotted to receive drug on a monthly or every-6-week basis. Even 20% of some drugs can equal $400 out of pocket for a patient, and, if both eyes are being treated, this translates into $1000 per month for treatment. Ultimately, insurance plans and the patient's socioeconomic background play a pivotal role in treatment decisions.

Dr. Benz: The best option when discussing treatment plans and cost is to be open and honest with the patient. In addition to a recent diagnosis, your patient has a whole host of concerns that are entering his or her mind, and it is important to guide them in making the best decision possible regarding treatment. Some patients may have a particular insurance that is very slow in covering new treatment; having this information can be helpful when choosing a treatment. ■




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