Clinical Endpoints for Retinal Disorders

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Before any drug can be approved, marketed, and sold in the United States, it must undergo extensive testing in large, multicenter clinical trials to demonstrate efficacy and safety. Approval is predicated on the successful achievement of endpoints in clinical trials, so the selection of appropriate endpoints is critical to the development of new therapeutic agents. For any clinical trial, the efficacy endpoint chosen must be clinically meaningful or relevant in order to be deemed acceptable by a regulatory agency. With respect to ophthalmic clinical trials, this may be a cure or improvement of a disease as defined by resolution or improvement of a patient’s signs and symptoms, visual function, or a change in an anatomic structure that has been correlated with visual function.

Although developing standards for clinical trials in ophthalmology sets a basis for meeting adequate safety and efficacy outcomes, the evolution of medicine requires that these standards be continually reviewed and potentially updated. In addition to providing clinical information to physicians, sophisticated new technologies have the potential to identify onset or progression of retinal diseases by providing new information on structural changes, which may lead to better visual outcomes for patients. Although these technologies may not yet be validated as being correlated with visual function, they provide detailed structural information and are useful in detecting improvements in early drug studies. In this column, we review what it means to choose efficacy endpoints for diseases of the posterior segment and highlight the importance of choosing endpoints that can appropriately assess the safety and efficacy of a new drug.

DEVELOPING ENDPOINTS

Efficacy endpoints are the crux of any clinical trial, as they assess the effectiveness of the study intervention. For the study result to “be acceptable to the medical community, the endpoint needs also to be meaningful—of either demonstrated or accepted relevance for the population and interventions of the trial.” Other characteristics to consider include the feasibility of measuring the endpoint, the reliability of the endpoint measurement, and whether the endpoint is sensitive to treatment differences and resistant to bias of both the study subject and the study personnel assessing the endpoint. The US Food and Drug Administration (FDA) recommends multiple measures of visual function as adequate primary endpoints when evaluating the safety and efficacy of new ophthalmic drugs. Some of these primary endpoints include visual acuity (ability to resolve high contrast visual angles), visual fields (threshold detection of a light source emanating from different locations), color vision (ability to distinguish among different wavelengths of light), and contrast sensitivity (ability to distinguish among different amplitudes of the same wavelength of light). The FDA acknowledges that degradation of these parameters forecasts worsening of functional vision that will in turn affect the patient’s quality of life. Although trial sponsors always have the option of pursuing different endpoints, it is the responsibility of the sponsor to then justify the clinical relevance of the new endpoint. Effectiveness of a treatment is demonstrated when there is a sufficient change in an endpoint that has been determined to be clinically meaningful. Treatments can also be considered effective if the endpoints remain stable, indicating protection from a clinically relevant decline in vision that is expected to occur over the observational period of a trial. At the end of the day, approval will ultimately be based on the risk/benefit ratio of the intervention and a combination of its efficacy and safety.

ANATOMIC MEASURES

Of particular interest for retinal disorders are measures that document improvements in a patient’s daily living and quality of life. Although the FDA currently recommends that study sponsors use change in visual function as a primary endpoint in measuring the effect of a new treatment for the eye, anatomic measures such as retinal detachment, the extent of spread of cytomegalovirus (CMV) retinitis, the extent of spread of geographic atrophy (GA) expansion, or the presence of vitreomacular adhesion (VMA) can also indicate the progression of a disease.

Anatomic endpoints allow for a measure of biologic activity that visual function assessments may not necessarily pick up, and they can be used as surrogate outcomes provided that the validated surrogate implies a result on the true endpoint of interest. The key word here is validated: for the FDA, this means that a structural endpoint shows a
Strong correlation to current vision or future vision (gain or loss). For example, many clinical studies are now looking at endpoints for GA that represent clinically significant study outcomes. GA, the advanced atrophic form of age-related macular degeneration (AMD), is a significant cause of both moderate and severe central visual loss. In GA, visual acuity change is often an underestimate of disease progression because, in early GA, the fovea may be spared while scotomas surrounding the fovea enlarge and interfere with reading and other tasks. Further, it has been demonstrated that for eyes with GA and visual acuity between 20/80 and 20/200, the reading rate is inversely correlated with the size of the GA. Patients have further reductions in reading rate as the GA area enlarges. Inherently, the area of atrophy measured by fundus photography is a useful endpoint for clinical trials because an intervention that would slow or halt the progression of GA would have a positive impact on daily living activities. This is of utmost importance because, if GA continues to progress, it will eventually reach the fovea, leading to almost certain vision loss.

Trials for other retinal diseases, such as vitreomacular adhesion (VMA), are also utilizing anatomic measures as clinically relevant endpoints. Occurring as a result of pathologic posterior vitreous detachment, VMA can lead to the development of traction-related complications such as macular holes, AMD, retinal vein occlusions, and diabetic macular edema. In recent VMA clinical trials, primary endpoints have included the release of vitreomacular traction, resolution of VMA, and changes in central macular thickness as measured by optical coherence tomography (OCT). Anatomic measures, such as structural endpoints, are useful because they provide an objective measurement that can be assessed in the clinic by a number of noninvasive imaging modalities that have been developed specifically for diseases of the eye. Determining the clinical relevance of anatomic endpoints is especially important when testing new therapies for slowly progressing diseases, in which tissue damage can precede vision loss by several years. And yet, the validation of anatomic measures for slowly progressing diseases is inherently a slow process, requiring rigorous and reproducible research over the course of many years.

New diagnostic technologies such as spectral-domain OCT and fundus autofluorescence provide ophthalmologists with an enhanced view of the eye and are gaining attention worldwide. Some new devices are capable of producing 3-D reconstructions, topographic analyses, and macular thickness measurements to reveal retinal disease. Another addition to the technology realm is the advent of ultrawide-angle fluorescein angiography. The ability to image the peripheral retina provides a more comprehensive assessment of the extent of a retinal disease process. A more complete picture of retinal health may also detect abnormalities that alter a treatment plan based initially on a clinical examination and traditional angiography. The use of adaptive optics scanning laser ophthalmoscopy (AO-SLO) has also improved imaging in the retina frontier as it images the retina in real time. This technology utilizes adaptive optics to remove optical aberrations from images obtained from SLO of the retina. Reducing aberrations allows the numerical aperture to be maximized, increasing light collection and improving both lateral and axial resolution. Furthermore, AO-SLO provides high resolution for clear visualization of individual photoreceptor cells. There is no doubt that these newer technologies are providing unprecedented information to clinicians, and, although they are not yet able to provide approvable endpoints, they offer more precise information on structural changes for proof-of-concept endpoints in early clinical studies.

CONCLUSION
Choosing the proper efficacy endpoints plays a key role in the overall design of a clinical trial and the future of the investigational treatment. Although a vision endpoint is the most important determinant of the efficacy of a drug, novel endpoints may be necessary in the design of ongoing and future clinical trials assessing treatments for retinal diseases.

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