Diagnostic imaging can reveal new clinical endpoints but validation is required

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in Berlin

NEW diagnostic technologies provide ophthalmologists with an increasingly detailed view of the eye, revealing features of ocular pathology that were undetectable by older techniques. The validation of changes in the newly detectable anatomical features as endpoints for clinical studies was the subject of a panel discussion at the 6th International Symposium on Ocular Pharmacology and Therapeutics.

Determining the clinical relevance of anatomical endpoints is especially important when testing new drugs for the treatment of slowly progressing diseases, such as glaucoma and diabetic retinopathy, where tissue damage can precede visual loss by several years, said Sara Krupsky MD, Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Israel, who chaired the discussion.

"We have many ways to follow visual function which are already well standardised but whenever vision is failing it is the end of a chain of events. We almost always detect tissue damage before visual function is diminished. The questions are: what is the relationship between tissue damage and vision loss? What is the relationship between structure and function?"

Apart from tests for visual function, the majority of current clinical endpoints are gross anatomical markers that are detectable by conventional ophthalmoscopy, said Wiley Chambers MD, deputy director of the FDA's Division of Anti-infective and Ophthalmology products.

Such endpoints include retinal detachment and the extent of spread of CMV retinitis, anatomical features that are unequivocally related to visual loss. The advent of newer technologies has revealed many previously undetectable features of ocular pathology, but their precise relationship to visual loss has yet to be elucidated, Dr Chambers pointed out.

"While we like to see function improved, in general, anatomic endpoints are better than functional endpoints. But there are certain key questions that are important when we deal with imaging instead of function. Those questions can be summarised as whether a change in structure will predict a functional change and whether you can image an anatomical change and relate that to vision."

There are several anatomical endpoints now under review that may be useful as indicators of disease progression or non-progression, he noted. They include retinal thickness in macular oedema and the dimensions of lesions in geographical atrophy.

Panel members discussing imaging endpoints for clinical studies (left to right): Drs R Zeimer, W Chambers, S Krupsky, R David and M. De Smet

In the case of macular oedema, it still remains to be determined how thick the retina needs to be and how long the thickness must be present before irreversible damage to the retina occurs. In the case of geographic atrophy it will be necessary to determine how much each individual lesion affects vision, Dr Chambers said.

Validation requires intensive research

The validation of an anatomical feature detected by imaging technology as an endpoint for clinical studies requires rigorous and reproducible research involving hundreds of patients over many years. Such validation often requires a 90-100% correlation between the endpoint and visual function, Dr Chambers noted.

An example of such research is a 10-year study by the NEI which was able to show that in patients with diabetic retinopathy, a three-step change on the EDTRS scale over a three-year period correlated with a reduction in a moderate three-line vision loss. The ETDRS grading system represents the degree of retinopathy with a number, based on findings obtained with diagnostic imaging.

"Consequently, that three-step change is a legitimate anatomical marker and the FDA has been able to use this as a clinically significant change, and we don't need to compare visual acuity changes."

Funding difficult for long-term research

The FDA's acceptance of markers for severity of disease as endpoints places a new onus on the pharmaceutical industry and the research community to identify similar anatomical markers for other slowly progressive diseases, said Ran Zeimer PhD, Johns Hopkins School of Medicine, Baltimore, Maryland, US.

"We need to invest in longitudinal studies. For example, in macular oedema there is no study that shows how the thickness of the retina affects visual function. It's down to us in industry and the research community to answer these questions. We need to address the same issues with regard to neuroprotection in glaucoma and vascular changes in AMD and the only way I think we can do this is with longitudinal studies."

Dr Krupsky concurred that the pharmaceutical industry should incorporate new diagnostic technologies into their studies to identify new anatomical endpoints. She noted, however, that the use of as yet unvalidated endpoints could create some confusion in interpreting the findings of clinical studies.

"I think the industry is the only one who can take on such a burden using a significant number of patients in order to use imaging technology to shorten the time necessary to arrive at an endpoint. But when using diagnostic imaging to detect unvalidated endpoints, you may get results that you don't expect in agents that would have been approved without this additional confusing data."

Public funding of such research might be the ideal option, since it would remove most conflicts of interest. However, such undertakings are beyond the reach of most institutions, said Marc de Smet MD, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

"It is getting more difficult to finance the studies necessary to validate technology. It would be very difficult with the staff I currently have to conduct a study where we need to prospectively follow 200+ patients over a five- or six-year period. In the Netherlands if I want to run such a study on my own, I need to get a minimum of €70,000 to €100,000 per year for personnel costs, and we are not even including the costs of new technology. I would have to approach a number of agencies to get the needed financial support – a time-consuming process."

Endpoints and evolving technologies

Dr de Smet also queried whether each new technology would have to be validated with respect to a given endpoint. Dr Chambers responded that once an anatomical marker has been identified as being related to visual function or disease severity it will remain a valid endpoint for all diagnostic imaging techniques that can faithfully detect it.

Dr Chambers added that the use of new diagnostic imaging in long-term studies, such as the AREDS trial which is now approaching 10 years, will offer a great boon to ophthalmological science in that it will provide not only endpoints for use in pharmacological studies, but will also provide a new insight into the pathology of eye diseases.

"From my perspective the AREDS study is potentially very valuable not because of what it showed or didn't show with respect to antioxidants, but because it will have followed 4,600 patients for 10 years with macular degeneration. It will, therefore, provide a very valuable data set of the natural history of the disease, and we will at some point be able to go back and look at what particular markers were most indicative of progression, assuming they were captured in the first place."

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