The role of optical coherence tomography (OCT) in characterizing normal and pathologic retinal architecture is still evolving. Numerous groups have tried to use OCT findings of retinal features as a surrogate for visual acuity in macular edema, but no traditional measure consistently accounts for visual outcomes. Retina specialists are still trying to process the data in the literature regarding this topic, as no good review currently exists.

Dilraj S. Grewal, MD, and Glenn J. Jaffe, MD, provide us with an overview of the literature and focus on the role of disorganization of the retinal inner layers (DRIL) as an OCT biomarker in various causes of macular edema. In this article, they will summarize the relationship of DRIL in diabetic macular edema and uveitic cystoid macular edema and discuss its impact on management of these patients.

DRIL can be a useful clinical biomarker if the imaging quality is sufficient to assess retinal layer boundaries. This can be challenging in certain scenarios like chronic macular edema. The current research will become increasingly useful as adaptive optics and OCT angiography improvements in processing algorithms and image resolution continue.

I am certain that the insights and expertise that Drs. Grewal and Jaffe share will be very helpful as we apply the OCT-characterized anatomy of the retina into treatment algorithms to optimize management of our patients.

Macular edema is an important cause of reversible visual acuity (VA) loss both in uveitis and diabetic retinopathy. Persistent macular edema may, however, lead to irreversible disruption of the retinal neural architecture, atrophy, and permanent VA loss. It is important to recognize the eyes with macular edema that may be predisposed to retinal neurodegeneration, as retinal tissue integrity is a measure of preserved axonal connections and an indicator of visual function.

In both uveitic cystoid macular edema (CME) and diabetic macular edema (DME), several possible optical coherence tomography (OCT) parameters have been evaluated as VA surrogates, including external limiting membrane (ELM) and ellipsoid zone (EZ) integrity, hyperefractive foci (HRF), cystoid spaces in the outer plexiform layer (OPL) and inner nuclear layer (INL), subretinal fluid, and the pattern of macular edema (cystoid versus diffuse).

However, none of these measures consistently accounts for visual outcomes. Accordingly, there is an unmet need for a reliable anatomical biomarker as a VA surrogate in macular edema. A recently recognized OCT parameter is disorganization of retinal inner layers (DRIL), which is defined as derangement of the normal laminar inner retinal structure. Sun et al. were the first to show that DRIL correlated with worse VA and had prognostic value in DME. Subsequent reports confirmed this relationship in both DME and uveitic CME, suggesting its role as an important VA surrogate.

In this review, we summarize what we have learned about the relationship of DRIL with VA in DME and uveitic CME and dis-
cuss its practical impact on management of such patients.

DEFINING DRIL

DRIL is the failure to identify any of the boundaries of the ganglion cell layer-inner plexiform layer (GCL-IPL) complex, INL, and OPL (Figure 1). Various studies have used the central 1,000-µm to 3,000-µm foveal area to measure the horizontal extent of DRIL based on this definition. The GCL-IPL is evaluated as a single-layer complex.

DRIL is assessed independently of intraretinal cysts, epiretinal membrane, subretinal fluid, or any other OCT-evident pathology. Intra-retinal cysts are commonly seen in the outer nuclear layer, resulting in overall retinal thickening; however, if the inner retinal layers can still be demarcated, then DRIL is not considered present. In addition, loss of the normal foveal contour does not constitute DRIL by itself unless there is concurrent loss of retinal layer boundaries.

DRIL IN DIABETIC MACULAR EDEMA

Sun et al. first showed that DRIL in the 1,000-µm foveal area was associated with worse VA, and that change in DRIL predicted future change in VA. They reported that greater DRIL extent at baseline correlated with worse baseline VA. A 300-µm increase in DRIL during a 4-month period was associated with a one-line worsening of VA at 8 months. If DRIL worsened by 250 µm or more at 4 months, no eye improved by one or more lines at 8 months and, conversely, if DRIL improved by 250 µm or more at 4 months, no eye worsened by one or more lines at 8 months.

The association of DRIL with worse VA held true even despite DME resolution or, conversely, in eyes with good vision despite concurrent edema. A history of anti-vascular endothelial growth factor (VEGF) treatment during the study period did not influence the association of foveal DRIL with VA. They showed absence of paradoxical VA change (worsening VA despite resolving DME) in eyes with DRIL change greater than 500 µm, suggesting that there is a threshold of DRIL worsening beyond which eyes are likely to lose vision, a finding that has important implications on the timing of therapeutic interventions.

Radwal et al. demonstrated that resolution pattern of DRIL was associated with subsequent VA after DME.
Figure 2. Serial optical coherence tomography (OCT) images of the central 1,000-µm foveal area showing the presence of disorganization of retinal inner layers (DRIL) (white arrow), along with intraretinal cysts and subretinal fluid in an eye with uveitic cystoid macular edema (CME), with a decline in vision to 20/60 (top). There is persistence of DRIL (white arrow) upon resolution of the CME (bottom), limiting the visual recovery to 20/40.
After adjusting for baseline VA, the VA change was best associated with DRIL change in an 8-month period during which DME resolved. Eyes in which DRIL resolved, either early or late, had improved VA deficit at 8 months compared to eyes with persistent DRIL.

DRIL has been also associated with capillary nonperfusion. Nicholson et al. showed that DRIL predicted areas of macular capillary nonperfusion on fluorescein angiography in eyes with diabetic retinopathy with 84.4% sensitivity and 100% specificity. However, there were some false-negatives; some cases had no DRIL despite angiographic capillary nonperfusion. Spaide showed that in eyes with treated DME, abnormalities of the retinal perfusion in both the superficial and deep plexus on OCT angiography.
Figure 4. A 45-year-old female with birdshot chorioretinopathy. Fluorescein angiogram shows petaloid leakage and perivascular leakage (top), and there is cystoid macular edema on optical coherence tomography without significant disorganization of retinal inner layers (DRIL) (middle). Following treatment with periorcular steroids and systemic immunosuppression, the macular edema resolves and there is no residual DRIL. The visual acuity improved from 20/60 to 20/20.
ography colocalized with DRIL. Balaratnasingam et al. recently demonstrated a significant positive correlation between the foveal avascular zone area on OCT angiography and DRIL length in both diabetic retinopathy and retinal vein occlusion, suggesting that vasculogenic insults at the level of the inner retina can also result in DRIL.

**DRIL IN UVEITIC CYSTOID MACULAR EDEMA**

We recently evaluated the relationship of DRIL in eyes with uveitic CME using data from the VISUAL I phase 3 trial. We found that eyes with DRIL had worse VA than those without DRIL. Greater horizontal and vertical DRIL extent correlated strongly with worse VA in eyes with various uveitis diagnoses and across a broad range of visual acuities and CME severity. Foveal DRIL (DRIL involving > 500 µm of the central foveal 1,000 µm) was also significantly associated with VA (Figures 2 and 3).

In addition to DRIL, central subfield thickness, area of intraretinal cysts, length of disruption of EZ, and presence of HRF also were highly associated with VA. We found that larger cysts strongly impacted VA. We also found a lack of significant association of DRIL with VA in multiple regression analyses, partly due to the strong association with intraretinal cysts, suggesting that similar to DME, there are multiple anatomical factors contributing to decreased VA in uveitic CME. It is possible that small cysts distort neurons without exceeding their mechanical limits, unlike larger cysts, and thus do not impact vision to the same extent. Future studies in uveitic CME are needed to help confirm the prognostic value of DRIL on VA and its reversibility potential.

**WHY DRIL MATTERS IN EVERYDAY PRACTICE**

Although the exact mechanism by which DRIL affects VA is still unknown, there are several possible explanations. DRIL is thought to correlate to regions where bipolar, horizontal, and amacrine cell synaptic connections have been disrupted, thus interrupting the transmission pathway between the photoreceptors and ganglion cells. Neuroglial degeneration as sequelae of inflammation, ischemia, or both may occur in macular edema and manifest as DRIL.

It is plausible that the neurosensory retina has a degree of elasticity and as long as the fluid pools within the elastic limits, the continuity of bipolar cells is maintained and the synapses remain viable. However, if the edema exceeds the elastic limits, bipolar axons snap, compromising this transmission pathway, which may explain why VA may not fully recover even following resolution of macular edema.

DRIL is a predictive biomarker for VA and is also useful for stratification of eyes with regard to a high likelihood of future VA improvement or decline (Figures 4 and 5). Although further histological correlation is needed, decreasing DRIL represents anatomic improvement toward more normal morphology. It is quite possible that the reversibility potential of DRIL declines with
increasing duration. This potential reversibility time limit would have important implications when one decides when to initiate therapy, for example with intravitreal anti-VEGF injections. A DRIL irreversibility time threshold may also offer new insights in patients with macular edema who are considered nonresponders.

Current work has laid the foundation for imaging tools such as OCT angiography and adaptive optics to evaluate neural degeneration in macular edema. Algorithms for automated DRIL grading and quantification of change would make it easier to use DRIL as a biomarker in clinical and research studies.

LIMITATIONS OF DRIL

For DRIL to be a useful clinical biomarker, the image quality must be adequate to assess retinal boundaries. In uveitic CME, inflammation may confound the assessment of DRIL due to media opacities, a challenge that was seen in nearly 30% of eyes in our series and may be more evident than in eyes with DME. DRIL may also be a generic finding of tissue damage from ischemia, and similar loss of retinal lamination has also been observed following retinal vein or artery occlusion, acute retinal necrosis, and blunt ocular trauma. In most studies, however, when using multivariate predictive models that considered other OCT variables, DRIL was not associated with VA, suggesting that DRIL may not be the sole contributor toward ischemia and VA loss.

CONCLUSION

Although several questions remain to be answered, DRIL has been established as an easily obtained, robust imaging biomarker that is predictive of VA in eyes with diabetic and uveitic macular edema. It can be easily incorporated into daily clinical practice as a valuable tool for patient counseling. The development of DRIL should be considered in the timing of therapeutic intervention given the reversibility potential of DRIL.

REFERENCES


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