

Ophthalmology Update

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Lauren A. Dalvin, M.D.

Many Ophthalmic irAEs Can Be Treated Without Discontinuation of Life-Prolonging Immunotherapy

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death protein 1 (PD-1) and programmed death ligand-1 (PD-L1). ICIs harness the host's immune system for anti-tumor activity.

“A wide range of immune-related adverse events (irAEs) have been documented with the increasing use of ICIs,” says Lauren A. Dalvin, M.D., Ophthalmology, at Mayo Clinic in Rochester, Minnesota. “Although ophthalmic irAEs are rare, it is vital that ophthalmologists recognize irAEs and understand their treatment, so life-prolonging ICIs can be continued.”

Dr. Dalvin and fellow researchers hypothesized that most ophthalmic irAEs can be managed with targeted therapy and should not require cessation of immunotherapy. To investigate, they identified the frequency of ophthalmic irAEs and need for ICI cessation for patients receiving a variety of currently available ICIs.

Researchers reviewed records for patients who received ICI therapy at Mayo Clinic in Minnesota from Jan. 1, 2010, to Feb. 29, 2020. Their study compared demographics, cancer diagnosis, prior ICI therapy, clinical features and outcomes among checkpoint targets, including CTLA-4 (ipilimumab), PD-1

(pembrolizumab and nivolumab), PD-L1 (atezolizumab, avelumab and durvalumab), and combination therapy consisting of ipilimumab and nivolumab. The study results were published in the *British Journal of Ophthalmology* in 2021.

RESULTS

Of the 996 patients who received ICI therapy, 28 (2.8%) experienced an ophthalmic side effect that came to the attention of an eye care provider.

The ICI that most often preceded side effects was pembrolizumab in 12 (43%) patients, followed by nivolumab in six (21%) patients, atezolizumab in four (14%) patients, ipilimumab and nivolumab combination therapy in four (14%) patients, avelumab in one (4%) patient, and ipilimumab in one (4%) patient. “The most frequent ICI preceding adverse effects was pembrolizumab; however, it was also the most commonly prescribed ICI, used by 475 of 996 patients,” notes Dr. Dalvin.

The most common side effect was dry eye in 16 (57%) patients, followed by uveitis in four (14%) patients.

Patients with ophthalmic side effects associated with PD-L1 inhibitors had a greater frequency of ocular surface adverse effects. Patients with ophthalmic side effects associated with combination therapy had a

higher frequency of hepatitis as a concurrent systemic adverse effect.

Follow-up was available in 13 (46%) patients. The ophthalmic side effects were controlled without discontinuing therapy in 12 (92%) of these patients. ICI cessation was required in one patient with panuveitis. “Most irAEs were either well controlled or resolved with targeted treatment, such as topical, periocular and systemic corticosteroids for inflammatory effects and artificial tears, topical cyclosporine and punctal occlusion for dry eye,” notes Dr. Dalvin.

There were no differences between ICI groups in the following:

- Affected eye
- Sex
- Race
- Type of primary cancer
- ICI therapy
- Duration of ICI use prior to presentation with the ocular side effect
- Length of follow-up
- Need for treatment for ophthalmic event

- Treatment outcome
- ICI discontinuation for ophthalmic adverse event
- Frequency of concurrent systemic adverse effects
- Final visual acuity

“Ophthalmic irAEs are rare but could be more common than previously estimated,” says Dr. Dalvin. “Our research indicates that most ophthalmic events, however, can be treated with targeted therapy without discontinuation of life-prolonging immunotherapy. It is crucial that ophthalmologists maintain a high index of suspicion for these adverse effects and, if necessary, carefully weigh the risks and benefits of discontinuing life-prolonging therapy in communication with the patient’s medical oncologist.”

FOR MORE INFORMATION

Fortes BH, et al. Ophthalmic adverse effects of immune checkpoint inhibitors: The Mayo Clinic experience. *British Journal of Ophthalmology*. 2021;105:1263.

Mobile Platform Obtains Quantitative Measurements of Exophthalmos With Variability Similar to Hertel Exophthalmometry



Andrea A. Tooley, M.D.

Hertel exophthalmometry is the most commonly used modality for measurement of globe position, which is important to quantify the amount of displacement caused by orbital disease. Sometimes, however, a Hertel device is not readily available. “We wondered whether a mobile application might provide an alternative measuring strategy,” says Andrea A. Tooley, M.D., Ophthalmology, at Mayo Clinic in Rochester, Minnesota. To test that concept, Dr. Tooley and fellow researchers compared the reliability of a novel exophthalmometry method that uses a smartphone platform to current standards.

MOBILE EXOPHTHALMOMETRY DEVICE

The mobile exophthalmometry device employs a readily accessible mobile ruler application that digitally extrapolates unknown static measurements based on known values. The researchers used it to obtain measurements of axial globe position through sagittal facial photos obtained with

the patient holding a standard credit card (known measurement) midline and parallel to the apex of the cornea, while the observer and cellphone camera were positioned at a 90-degree angle to the plane of the credit card (Figure, see page 3).

The lateral orbital rim and apex of the cornea were used as landmarks. The distance between the two was determined by manually identifying the landmarks with the measuring arrow, which generated a calibrated 2D measurement based on the credit card width.

Multiple independent measurements were obtained from a single photo by each observer to report the interobserver and intraobserver reliability. Observers repeated mobile measurements 2 to 4 times on each patient photo over a period of six months.

THE STUDY

The prospective, comparative study included 50 patients (99 eyes) for a total of

594 mobile measurements between two observers. The study included patients with extreme exophthalmos as well as enophthalmos after orbital fractures and trauma to represent variability and evaluate limitations at extremes of measurement.

The intermodality correlation and agreement between Hertel and mobile exophthalmometry and the intraobserver and interobserver reliability with repeated mobile measurements were the main outcomes.

RESULTS

Researchers found no significant difference in the measurements obtained by Hertel and mobile exophthalmometry. There was a strong linear correlation between Hertel exophthalmometry and mobile exophthalmometry with a Pearson correlation coefficient of 0.910 and 0.888 for the right and left eyes, respectively. Bland-Altman plot analysis showed excellent agreement between the two modalities.

The mobile exophthalmometry platform demonstrated high intraobserver reliability with a Cronbach's alpha of 0.992 and 0.985 for the right and left eyes, respectively. An intraclass correlation coefficient of 0.992 (95% confidence interval, 0.987-0.995) for the right eye and 0.986 (95% confidence interval, 0.978-0.991) for the left

eye demonstrated excellent reliability between observers.

Dr. Tooley notes: "Study results demonstrate strong correlation between Hertel and mobile measurements. Even novice observers obtained accurate measurements for most photos. Extensive user education and experience may not be required.

"Pre-labeled reference and measuring arrows are automatically generated following the acquisition of the photograph for immediate measurements, and unmeasured photographs may be stored and measured at a later time.

"Although a 2D measurement does not replace the 3D view of Hertel exophthalmometry, this simple-to-use mobile application yields reliable, accurate measurements in a timely, efficient manner — and may be a suitable alternative when Hertel exophthalmometry is not available."

Study results were published in *Orbit* in 2021.

FOR MORE INFORMATION

Magazin M, et al. Utilizing a mobile platform to obtain quantitative measurements of exophthalmos. *Orbit*. In press.



Figure. Sagittal facial photos with standard credit card reference show exophthalmometry measurements generated with smartphone application. Based on *Orbit*.

Optic Effect on Peripheral Retinal Illumination Holds Implications for Negative Dysphotopsia

Negative dysphotopsia (ND), an unwanted shadow in the temporal field after cataract surgery, occurs in approximately 12% of patients at one month after surgery, decreasing to 3% at one year. ND is a major source of patient dissatisfaction.

The intraocular lens (IOL) is thinner and smaller in diameter than the natural crystalline lens, and when placed in the capsular bag, a space is created between the posterior iris and the IOL that is not present in the phakic eye. These characteristics provide an opportunity for peripheral light rays to miss the IOL and nonphysiologically illuminate the peripheral retina. Additionally, a narrow shadow-like region may form in the nasal retina, bounded anteriorly by light missing the IOL and posteriorly by light refracted by the IOL. This shadow in the nasal retina

is hypothesized to correspond to the bothersome temporal shadow seen in ND (Figure, see page 4).

"It is thought that the perception of the ND shadow may be mitigated if the dark region of nasal retina is illuminated by redirected light, or if light missing the IOL is shifted anteriorly off the retina, or both," notes Michael A. Mahr, M.D., Ophthalmology, at Mayo Clinic in Rochester, Minnesota.

A recent clinical study by M. K. Bonsemeyer and others, published in the *Journal of Cataract & Refractive Surgery* in 2022, showed that enlarging an IOL hydrophobic optic from 6.0 mm to 7.0 mm significantly reduced ND symptoms at one month after cataract surgery. Based on those findings, Dr. Mahr and fellow researchers conducted a laboratory study



Michael A. Mahr, M.D.

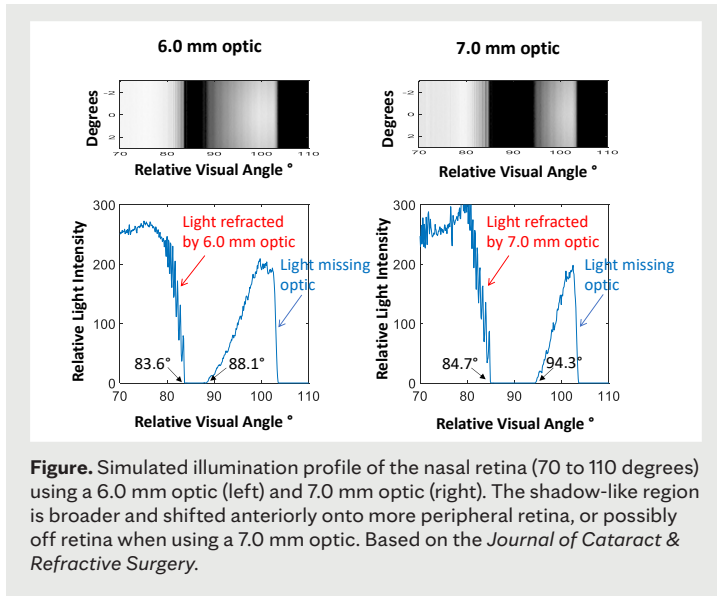


Figure. Simulated illumination profile of the nasal retina (70 to 110 degrees) using a 6.0 mm optic (left) and 7.0 mm optic (right). The shadow-like region is broader and shifted anteriorly onto more peripheral retina, or possibly off retina when using a 7.0 mm optic. Based on the *Journal of Cataract & Refractive Surgery*.

“Consequently, the distinct narrow shadow seen with a 6.0 mm optic is enlarged and shifted peripherally with a larger 7.0 mm optic,” says Dr. Mahr.

Calculations for a high-refractive-index optic showed similar changes. The shadow width increased from 5 degrees to 10 degrees, with the outer edge of the shadow moving peripherally 6 degrees.

using ray-tracing analysis to compare the influence of 6.0 mm and 7.0 mm IOL optic diameters on illumination of the peripheral retina. Their study was published in the *Journal of Cataract & Refractive Surgery* in 2022.

The researchers used Zemax OpticStudio software to generate simulated retina illumination profiles of the peripheral retina for an average pseudophakic eye with an in-the-bag biconvex IOL and a 2.5 mm pupil. Researchers compared ray-tracing diagrams and simulated retina illumination profiles using 6.0 mm and 7.0 mm optic-diameter IOLs. Retinal locations were scaled to relative visual angles from 70 to 110 degrees horizontally.

RESULTS

A low-refractive-index 7.0 mm optic increased the focused image field by 3 degrees when compared with a 6.0 mm optic. The width of the shadow also increased from 7 degrees to 10 degrees, which moved the outer edge of the shadow more peripherally by over 5 degrees.

“Our simulated illumination profiles confirm that light focused by the IOL, as well as nonphysiologic light that bypasses the IOL, is shifted peripherally when using a 7.0 mm optic compared with a 6.0 mm optic,” says Dr. Mahr. “As a result, the narrow shadow seen with a 6.0 mm optic is broadened, and its anterior border is shifted onto more peripheral retina, or possibly off retina. This illumination change may be less bothersome or may allow easier neuroadaptation — thus explaining why ND rates are lower when using a 7.0 mm-diameter optic.”

FOR MORE INFORMATION

Bonsemeyer MK, et al. Dysphotopsia and functional quality of vision after implantation of an intraocular lens with 7.0 mm optic and plate haptic design. *Journal of Cataract & Refractive Surgery*. 2022;48:75.

Erie JC, et al. Effect of a 7.0 mm intraocular lens optic on peripheral retinal illumination with implications for negative dysphotopsia. *Journal of Cataract & Refractive Surgery*. 2022;48:95.

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Cover Image

Human multicolored iris of the eye animation concept
Credit: CG Alex

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