DEVELOPMENT OF THE LATEST ACCOMMODATIVE IOLS

OVER the years, the results of accommodative pseudophakic IOLs have been mixed, but that may be ready to change as the last frontier of ophthalmology may be tamed with new lenses that provide options for surgeons and hope for their patients. The future may be now as innovation is changing the way physicians look at accommodative IOLs.

Continues on page 20: IOLs

BIWEEKLY ANTI-VEGF TARGETED AS NAMD TREATMENT

INCREASED anti-VEGF dosing is a potential option for treating neovascular age-related macular degeneration that is refractory to chronic monthly injections. Researchers are finding a reduction in refractory intraretinal and subretinal fluid along with improvement in visual acuity after receipt of five biweekly doses.

Continues on page 32: VEGF

DEALING WITH POSITIVE, NEGATIVE DYSPHOTOPSIS

New lens designs may reduce problem for patients in future

By Fred Gebhart;
Reviewed by Nick Mamalis, MD

OPHTHALMOLOGISTS CANNOT discount dysphotopsias, either positive or negative, after cataract surgery and IOL placement. The literature suggests that dysphotopsias are relatively rare, but patient reports suggest a different story.

“If you ask patients, it can be almost 50% immediately after surgery,” said Nick Mamalis, MD, professor of ophthalmology at the University of Utah John A. Moran Eye Center in Salt Lake City. “The majority of these just go away or patients get used to them. But for an important minority of patients, these are significant visual issues and they don’t improve as time goes on.”

Positive dysphotopsias produce visual artifacts that appear as areas of bright light, streaks, and flashes central in the visual field. Negative dysphotopsias produce dark temporal shadows that mimic the effect of blinders worn by racehorses.

Both positive and negative dysphotopsias are associated with the IOL material, design and placement, Dr. Mamalis noted.

Positive dysphotopsias are most often characterized by persistent bright rings, flares, arcs, halos, and flashes that most often appear when light is coming into the eye from the side, such as the oncoming headlights of another vehicle. The long-term incidence may be as high as 1.5% and can vary greatly by IOL type, material, and design.

Continues on page 14: Dysphotopsias
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A closer look at pre- and post-thermal pulsation therapy

Patients undergoing cataract surgery may have better final results with treatment

By Cynthia Matossian, MD, FACS

I perform a lot of thermal pulsation therapy in patients undergoing cataract surgery. These patients deserve to have their tear film stabilized before surgery so their vision will be optimized after surgery. Thermal pulsation therapy can change surgical planning and outcomes. But even knowing that, many surgeons still struggle with how to talk about meibomian gland dysfunction (MGD) and MGD treatment in the context of cataract surgery.

What has helped me tremendously in educating patients are the meibography images from the LipiView device (Johnson & Johnson). These black and white images are easy for patients to understand. I show them their own pictures and compare to those of normal, healthy meibomian glands. I tell patients that we are fortunate to have a treatment to help the glands, although I am up-front about the fact that their glands will not look “brand new” again.

DRAMATIC DROP-OUT
When the drop-out is dramatic, it is an easy discussion with the patient. However, I take a different approach when the glands look normal. I review the importance of both structure and function of the glands with patients and point out that the inspissated glands, although they may look “normal,” are not producing meibum.

Then I say, “I have good news. You have great glands—but they are constipated.” It might sound funny, but this is a term patients easily understand. I explain, “We can now intervene, get the impacted material out, and you have a good chance for these glands to start functioning better because you have not lost any of the structure yet.”

Since MGD and inflammation are often concomitant, I also try to educate patients about tear film markers for dry eye, again using visual aids. The MMP-9 test (InflammaDry, Quidel) is a great educational tool. When the test is positive, I hand the test cartridge (which looks similar to a home pregnancy test) to the patient so they can see the red stripe. At the end of the exam I give them their tear osmolarity score and MMP-9 status.

Three months after thermal pulsation therapy, I bring the patient back for a follow-up exam. At that point, we repeat the MMP-9 and tear osmolarity testing (TearLab) and share those results with the patient. I don’t repeat the meibography at three months because they are not likely to see a big difference in gland structure that soon. I ask the patient to continue their oral omega-3 supplements (Xiidra) or Restasis (Allergan) if that is part of their treatment plan.

Thermal Pulsation Therapy

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Planned intervention changed in 40% of eyes post-thermal pulsation therapy. (Image courtesy of Cynthia Matossian, MD, FACS)

‘I always explain to patients that thermal pulsation therapy is not a ‘one-and-done’ procedure.’”

– Cynthia Matossian, MD, FACS

NOT ONE-AND-DONE
I always explain to patients that thermal pulsation therapy is not a “one-and-done” procedure. At 3 months, I perform a diagnostic meibomian gland expression and congratulate the patient on how much better their glands are functioning. I repeat meibography annually and plan to do the thermal pulsation treatment every 12-18 months.

Depending on the severity of the disease and the patient’s level of discomfort, I may opt to perform intense pulsed light (IPL) therapy on the lower lids at the six-month mark if the patient’s skin tone is between Fitzpatrick 1 and 4. (IPL cannot be performed on skin darker than Fitzpatrick 4).

Sometimes, I will perform a manual expression with TearCare (Sight Sciences) in between LipiFlow treatments. I find that IPL or TearCare can potentiate and extend the effect of the LipiFlow treatment.

These treatments are all adjunctive and “stackable” to achieve the desired therapeutic effect and reduce symptoms of discomfort for our patients.

Dr. Matossian did not indicate any proprietary interest in the subject.

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Bascom Palmer tops in annual program survey

New treatment reduces corneal oedema after cataract surgery

Considering BID ocular steroid post-cataract surgery

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3 Considering BID ocular steroid post-cataract surgery
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OCTOBER 15, 2019 :: VOL. 44, NO. 17

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Dust yourself off

When we get knocked down in our careers, we get back up

Thinking back on my own experience, I recall a brilliant colleague who applied for his first NIH grant only to receive an extremely critical review. Angry and disheartened, he vowed never to apply again. And he didn’t. Decades later, I believe he very much regrets that decision.

I wonder if this phenomenon applies to clinicians. One acquaintance, performing her first cataract extraction as a resident, had the patient experience a choroidal hemorrhage and the eye was blinded. She went on to become a better-than-average surgeon. Does early adversity in the operating room stimulate young surgeons to practice their surgical skills more than their colleagues whose first operations go smoothly?

Closer to home, I remember being a young and inexperienced department chair in California. I made a decision that didn’t produce the results I had hoped. I was disappointed and aware that the members of my department, who were depending on me to make sure things went well, would be disappointed. I told my dean, who was a very experienced and wise person whom I admired, and waited for him to criticize me. But he didn’t. “These things happen to all leaders,” he said. “You admit your mistake and take your lumps as people criticize you. Then you get back up, dust yourself off, go back to work, and do your absolute best.”

So the next time things don’t go your way and you find yourself getting a tad discouraged, dear reader, find “Tubthumper” on your phone app or tell Alexa to play it for you when no one else is around. Sing along in a loud voice and awaken within you “the resilience of ordinary people.”

The findings of the paper are instructive. A substantial percentage of the near-miss applicants gave up, with over 10% never again applying for NIH grants. But amongst those who persisted in the pursuit of NH research grants, over the long term the junior people who had a near miss in their first try proved to outperform those who narrowly won their first grant. The authors conclude that “early-career setback appears to cause a performance improvement among those who persevere” and believe their findings “are consistent with the concept that ‘what doesn’t kill me makes me stronger,’ which may have broad implications for identifying, training and nurturing junior scientists.”

REFERENCE
Xiidra® (lifitegrast ophthalmic solution) 5% blocks the interaction of ICAM-1 and LFA-1, which is a key mediator of the inflammation central to Dry Eye Disease. In vitro studies have shown that Xiidra may inhibit the recruitment of previously activated T cells, the activation of newly recruited T cells, and the release of pro-inflammatory cytokines.¹

**Indication**

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

**Important Safety Information**

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dyseusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

Safety and efficacy in pediatric patients below the age of 17 years have not been established.
BRIEF SUMMARY:
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

DOSEAGE AND ADMINISTRATION
Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single-use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

CONTRAINdications
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data
Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg /kg /day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg /kg /day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg /kg /day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

Lactation
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

Pediatric Use
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

NONCLINICAL TOXICOLoGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.

Mutagenesis: Lifitegrast was not mutagenic in the in vitro Ames assay. Lifitegrast was not clastogenic in the in vivo mouse micronucleus assay. In an in vitro chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.

Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD] of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.

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Physicians can dive into IOL parameters, platforms before making it a go-to technology

By David A. Goldman, MD; Special to Ophthalmology Times

Beyond relying on training, surgical skills, and experience, surgeons must have ultimate confidence in the technology they use in practice and the vision-correction strategy they recommend to patients. To incorporate IOL solutions that can provide outstanding, dependable, and consistent refractive outcomes requires understanding the attributes of each platform. Equally important is the ability to pivot when the clinical and scientific data warrant a change.

**ASPHERIC DESIGNS**

Companies have designed aspheric IOLs with an anterior prolate surface (Johnson & Johnson Vision), a posterior prolrate surface (Alcon), or with both anterior and posterior prolrate surfaces (Bausch + Lomb), and these models compensate for corneal SA to varying degrees. The Tecnis platform (Johnson & Johnson Vision) and AcrySof Restor (Alcon) aim to correct positive SA from the cornea. The enVista IOL (Bausch + Lomb) has zero SA and thus preserves the cornea’s natural sphericity profile. I favor this zero-sphericity approach because it provides my patients with an increased tolerance to defocus. When the cornea’s SA is completely neutralized, the patient will have good contrast sensitivity, but at the same time, will notice a trade off in terms of the limited range of clear uncorrected vision. For many patients, enVista functions with an excellent range—a big “sweet spot” to hit the intended refraction target.

Patients with previous hyperopic LASIK will have eyes already presenting with negative spherical aberration, implanting a zero sphericity IOL is a great choice, in my opinion. There is no concern with angle kappa, as the implant’s asphericity makes it more forgiving in its use. In patients with high angle kappa or lens decentration, a negative spherical aberration lens may produce suboptimal visual outcomes.

**DYSPHOTOPSIAS**

The enVista platform is associated with very low incidence of dysphotopsia. As Masket and Fram have discussed, the index of refraction and the surface reflectivity of lenses can be associated with positive dysphotopsia, meaning certain IOLs will show less of a tendency. Silicone and copolymer lenses tend to have a much lower incidence of positive dysphotopsia than acrylic lenses, Masket has said. In my experience, I have heard more glare and halo complaints from patients receiving implants other than enVista. There are reports of explanted lenses in the literature, and I have performed lens exchange due to the issue for a few patients.

**WHAT ELSE MATTERS?**

I like to know that an IOL’s material is glistening-free, with a very clear optic that will stay that way many years out. Even if the acuity is fine, an IOL that contains glistenings does not look as good in the eye, and in rare cases glistenings can affect vision. The enVista IOL is the only single-piece, hydrophobic acrylic implant available in the United States proven to be glistening-free. The material is difficult to scratch during loading, inserting, and manipulation. There is nothing more frustrating than performing a perfect cataract case and finding that the lens was inadvertently scratched during its placement in the cartridge.

Of course, with any type of toric platform, even a small amount of rotation is maybe damaging, dramatically effecting results (i.e., a 3% loss of correction effect for every 1 degree off). It is critical to patients’ outcomes to know that my toric choice is going to be rigid and stable. The enVista toric MX60T demonstrated excellent rotational stability, with 94.4% of subjects with 5° or less IOL rotation from close of case to 6 months post-op (data on file with Bausch + Lomb).

**CONCLUSION**

Refractive cataract surgery with premium IOL implants provides a unique opportunity for patients to achieve life-changing vision. However, not all lens platforms, including toric lens platforms, are created equal.
9 effective habits surgeons should adopt for best outcomes

List helps physicians establish a standard of care to follow throughout career

By Elizabeth A. Davis, MD, FACS; Special to Ophthalmology Times

FOLLOWING THESE NINE best-practice habits can help surgeons establish a standard of care for the countless surgeries they will perform throughout their careers, according to Elizabeth A. Davis, MD, FACS.

1. BE PREPARED
Identify ocular comorbidities that may present intraoperative challenges and have a game plan. Conditions like small pupils, intraoperative floppy iris syndrome, loose zonules/phacodonesis, dense brunescent rock-hard cataracts, white intumescent cataracts, and posterior polar cataracts all pose potential risks, need proper approaches, and require the possible use of assistive devices intraoperatively.

2. DISCUSS LENS OPTIONS
Discuss appropriate lens options for the patient and desired target refractive outcomes. Cataract surgery is refractive. Patients may have high expectations of fast and painless surgery as well as excellent visual results, including the possibility of reduced dependence on glasses. Offer elective options of premium IOLs. Have the ability to conduct enhancements when needed.

3. OBTAIN RELIABLE BIOMETRY, USE APPROPRIATE LENS FORMULAS.
This involves treating any pre-existing ocular surface disease (OSD), repeating axial length measurements when warranted for confirmation of differing eye lengths, and knowing which formula is suitable. Using the latest generation of multifocal variable formulas can enhance predictability of refractive results. Personalize A-constants for precise outcomes.

4. CONDUCT A TIME-OUT
Perform a time-out to confirm the correct patient, correct eye, correct procedure, and correct IOL.

5. ADJUST MACHINERY PROPERLY
Position the head, microscope, foot pedals, and portable instrument stand properly. The surgeon should be comfortable, have unencumbered access to the eye, be readily able to receive and pass instruments without looking away from the field, and continuously establish good focus, magnification, and centration.

6. BE EFFICIENT, BUT SAFE
Less time, phaco energy, and fluid in the eye is best, but do not rush. Hand movements and positioning should be precise and effective. Minimize the number of times instruments are placed in and out of the eye. Not only does this take more time, but each entry could introduce contamination and/or distort the wound.

7. TRAIN STAFF
Assistants should be familiar with the surgeon’s technique, set up, machine settings, and instruments. Standardize the process as much as possible, as this will benefit all involved. A well-performed cataract surgery is like a carefully choreographed dance—each team member provides a supportive-but-critical role in the performance, leading to efficient and ergonomic movements that avoid omitting steps or making errors.

8. REDUCE INFECTION
Use intracameral antibiotics to reduce the incidence of postoperative infection as supported by numerous studies on large numbers of patients.

9. PRACTICE SELF-EVALUATIONS
Learn from mistakes, colleagues, meetings, journals, and videos. This involves keeping up with advances in technology and trying new techniques/devices/IOLs. The field of cataract surgery (and ophthalmology, in general) is constantly advancing, and there is a need for continuous adaptation.

TAKE-HOME

« The field of cataract surgery is constantly advancing, and there is a need for continuous adaptation.»

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Dr. Goldman is a stockholder for Bausch Health Companies, Inc.

Dr. Davis is partner, Minnesota Eye Consultants, Bloomington, MD. She did not indicate any proprietary interests relevant to the subject matter.

OPTIONS

(Continued from page 9)

Dr. Davis is partner, Minnesota Eye Consultants, Bloomington, MD. She did not indicate any proprietary interests relevant to the subject matter.
I didn’t realize STARS were little dots that twinkled

—Misty L, RPE65 gene therapy recipient

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Cadaver eyes used to demonstrate capsular safety of hybrid phaco tip

Tool can be useful for both residents, experienced surgeons alike

By Steve Lenier; Reviewed by Liliana Werner, MD, PhD

POSTERIOR CAPSULE RUPTURE (PCR) is a common complication of cataract surgery, with most ruptures occurring during phacoemulsification, according to Liliana Werner, MD, PhD, professor of Ophthalmology and Visual Sciences and co-director of the Intermountain Ocular Research Center at the John A. Moran Eye Center, University of Utah.

Risk factors that increase the likelihood of this occurrence include surgeon experience, operative factors such as a small pupil (3 mm or less), and other comorbidities, such as pseudoexfoliation and diabetic retinopathy. With a rupture, there may be a loss of vitreous and a worse visual prognosis. Researchers performed a study using cadaver eyes to evaluate and the results of using a novel hybrid phacoemulsification tip with a polymer overmold.1

In 2006, Steven Dewey, MD, popularized a needle design with no sharp edges. Studies have shown this has helped reduce the incidence of PCR. The present study evaluates a smooth hybrid needle tip, with a polymer at the distal end made of a proprietary material.

STUDY DETAILS

The study compared this tip, with a balanced metal tip.1 Cadaver eyes were prepared with the Miyake-Apple technique, where the eye is sectioned and the anterior segment glued to a glass slide. This provides a posterior view of the entire capsular bag and zonular apparatus. In the first experiment, the tip was used with the bevel pointing down. In the first pair of eyes, the researchers determined the vacuum limit, and found that it could be raised up to 300 mm Hg without having PCR. They determined that for the study, the vacuum would be set to 150 mm Hg.

In the next four pair of eyes, still with the bevel down, the researchers began in each eye with one tip, and increased torsional energy in 5% increments up to 60%. If there was no rupture they switched to the other tip. In this test, the hybrid tip required more energy for PCR.

This is not representative of a surgical case because the bevel was down. In the second experiment, the bevel of the tip was kept pointing up. The same process was followed, a tip was inserted and the torsional energy was raised in 5% increments to a maximum of 60%, with a fixed vacuum of 150 mm Hg and flow rate of 30 cc/min. Again one tip was inserted, and if there was no rupture at 60% the researchers switched to the other tip.

The mean torsional power required for PCR was higher in the hybrid group. To determine if phaco would weaken the capsular bag without did a sub-analysis that excluded capsules that were reused, and the results remained significant.

FIGURE 1
A. The anterior view of a cadaver eye is seen, showing the capsular bag and zonular apparatus. B. The cadaver eye is sectioned using the Miyake-Apple technique, and the anterior segment is flued to a glass slide.

TAKE-HOME

> A needle with no sharp edges can help reduce the incidence of PCR, and a study has evaluated a smooth hybrid needle tip, with a polymer at the distal end.

VARIABLES INFLUENCING PCR

These six variables all influence PCR. Perhaps playing the most important role are numbers 1 and 5 on the list.

1 Pressure of the tip against the capsule
2 Amount of active vacuum
3 Aspiration flow rate
4 Gauge of the needle
5 Needle sharpness and degree of angulation
6 Energy modulation active at the time of contact

LIMITATIONS

The study results were significant, but it was performed in a small sample size, and was an ex vivo study only. It is difficult to have a true control in a cadaver eye study.

Efficiency must also be considered, as it may be a limiting factor in “safer” needles. Radius needles are slightly less efficient.

A ROLE FOR THE HYBRID TIP

The researchers concluded this tip can be useful for both residents and experienced surgeons, and noted that whoever is considering using it should consider all risk factors when choosing a needle tip.

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Dr. Werner has no financial disclosures related to this project.
FOR ROTATIONAL STABILITY, THERE’S NO COMPARISON


Please see Important Product Information on the adjacent page.
DYSPHOTOPSIAS

(Continued from page 1)

Positive dysphotopsia was first reported in polymethylmethacrylate (PMMA), the material most commonly used during the early development of IOLs. Symptoms were generally minor glare and transient.

Hydrophobic acrylic lenses are more prone to positive dysphotopsia. The higher index of refraction is more likely to result in internal reflections when exposed to bright sources.

Silicone lenses are rarely associated with positive dysphotopsia, possibly because of lens design. Lenses with square edges, typically hydrophobic acrylic IOLs, are associated with an increased incidence of positive dysphotopsia. Frosted and textured edges as well as beveled designs have been used to reduce the intensity of stray reflections and reduce the incidence of positive dysphotopsia.

Treating positive dysphotopsias is relatively straightforward. Explanting and exchanging the original lens with an IOL that has a different material or edge design usually reduces or removes the problem entirely. PMMA, silicone, and hydrophilic acrylic lenses with edge designs that are not square are reported to help resolve positive dysphotopsias.

“Negative dysphotopsias are completely different,” Dr. Mamalis pointed out. “The more often you ask about negative dysphotopsias, the more frequently patients report those dark temporal shadows, especially in the first couple of weeks.”

About 71% of negative dysphotopsias resolve in the first weeks and months after surgery, he continued. Depending on how and when patients are questioned, between 0.2 and 2.4% have persistent symptoms.

“Do not get too excited at first and try to do something about it immediately,” Dr. Mamalis advised. “In a lot of patients, it goes away.”

The etiology of negative dysphotopsias involves the spatial relationships between the IOL, the capsular bag, and possibly the iris. IOLs implanted in the capsular bag or in the posterior chamber are more likely to produce negative dysphotopsias while IOLs implanted in the sulcus or in the anterior chamber seldom do.

Ray tracing suggests that at least part of the problem lies with internal reflections when the lens is placed in the capsular bag that can cast temporal shadows. Other potential factors include corneal curvature, anterior chamber depth, IOL power, axial length, and the distance between the pupil and the implant.

“Negative dysphotopsias are seen more frequently in patients who have a square-edge IOL,” Dr. Mamalis said. “It can occur with any lens material, though we see it more frequently with hydrophobic acrylic.”

Treatment typically involves IOL exchange and implantation of a new lens into the sulcus. Piggyback or add-on IOLs can also help alleviate negative dysphotopsias by diffusing light more effectively before it enters the eye, reducing the potential for shadow formation.

Reverse optic capture, placing the optic over the edges of the capsular bag instead of in the bag, can also help. And some surgeons perform laser anterior capsulotomy to enlarge the capsule opening.

New lens designs may reduce the problem in the future. The Maskit lens, with a groove on the anterior surface, allows the lip of the optic to ride over the anterior capsule, reducing the potential for negative dysphotopsias. A bag-in-lens design serves the same purpose, putting the optic atop the bag rather than allowing the bag to ride over the edge of the optic.

Another design adds peripheral concavity to the optic to better diffuse light entering the eye, reducing the potential for shadows.

“The treatment varies,” Dr. Mamalis said. “Depending on the patient, changes in IOL material, design and placement can decrease or treat these dysphotopsias when they occur.”

POSSIBLE TORIC IOL RELATED DYSPHOTOPSIA

TORIC IOL IMPO...
New IOL design trends avoid negative dysphotopsias

Surgeon also uses primary reverse optic capture with positive outcome for patients

By Fred Gebhart; Reviewed by Samuel Masket, MD

DYSPHOTOPSIA MAY BE one of the most under-recognized complications following otherwise unremarkable cataract surgery. Based on subjective symptoms, up to 20% of patents have negative dysphotopsia (ND), a temporal dark shadow after IOL implantation. Other patients have positive dysphotopsia (PD), characterized by light streaks, arcs, central light flashing or star bursts. Some patients may have both ND and PD.

“Overall, dysphotopsia has not been studied particularly well, especially epidemiologically,” said Samuel Masket, MD, founding partner, Advanced Vision Care, and clinical professor of ophthalmology at the David Geffen School of Medicine, Stein Eye Institute, University of California, Los Angeles.

Early ND symptoms tend to improve over time due to neuroadaptation, but about 3% of cases will have chronic ND at one year after surgery.

PD is directly related to square-edge design and the index of refraction of an IOL. The higher the index of refraction, the more complicated the ND. It is a tempered dark arc, similar to the effect of putting blinders on a horse. Unlike PD, there is no good correlation between clinical findings and optical lab findings, Dr. Masket said.

Researchers have suggested that square edges can cast ND shadows where rounded edges do not. And some have indicated that ND is also associated with a greater iris to IOL distance and an expanded posterior chamber depth. However, these assertions are not supported in clinical investigations.

Studies reveal increased posterior chamber depth does not cause ND and that any IOL, irrespective of material or edge design, implanted in the capsule bag can result in ND, which resolves when the very same inciting lens is moved from the bag to the ciliary sulcus.

These findings suggest a relationship between the IOL and capsule bag as central to ND. “Historically, every intraocular lens on the market in the United States has been associated with ND,” Dr. Masket said. “While ND is likely multifactorial, it is prevented, relieved or improved when the IOL optic edge overlies the nasal capsulotomy, rather than the capsulotomy overlying the optic edge.”

Dr. Masket published reverse optic capture (ROC), either as a therapeutic or prophylactic measure for ND, in 2011. A 2018 update with ROC in 43 eyes showed very good success, he reported. Of 22 eyes with chronic ND, 21 were corrected with secondary ROC and 21/21 contralateral eyes successfully avoided ND using primary ROC. All of the eyes that underwent primary ROC placement had fibrotic PCO that required laser posterior capsulotomy within three months of the initial surgery.

Dr. Masket’s original lens was licensed and modified by Morcher. It has CE marking and is being developed as the model 90S.

Two other capsulotomy supported IOLs have been CE marked, he reported, the Tassignon “BIL” (Morcher) and Femtis (Oculentis). The Tassignon lens has had no reported ND in several thousand uses and the Femtis has had no ND in its reported series of 384 lenses. In addition to the absence of ND, capsulotomy-supported IOLs have a more predictable ELP, a stable toric axis, absence of capsule contraction, perfect centration when the capsulotomy is centered on the visual axis, reduced HOA and limited optic tilt. “There is likely a future for this design concept,” Dr. Masket concluded.

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This article is based on Dr. Masket’s presentation at the 2019 European Society of Cataract & Refractive Surgeons Congress. Dr. Masket is the patent holder for an anti-dysphotopic IOL that is being developed by Morcher GmbH.
PROGRESSIVE SOLUTIONS FOR

PRESBYOPIA

PRESBYOPIA-CORRECTING IOLS: EXPANDING, IMPROVING LAST FRONTIER

While work has just begun, physicians are seeing results

By Lynda Charters; Reviewed by Jorge Alio, MD, PhD

PRESBYOPIA-CORRECTING IOLS: EXPANDING, IMPROVING LAST FRONTIER

Presbyopia-correcting IOLs are among the most important recent innovations in cataract and refractive surgery. A number of options are available to satisfy a growing patient population that demands spectacle-independent intermediate vision in addition to distance vision.

“These technologies have resulted in tremendous changes in clinical practice,” said Jorge Alio, MD, PhD. “Selecting the appropriate presbyopia-correcting IOL is now a challenge for most ophthalmologists.”

PRESBYOPIA-CORRECTING IOL CHOICES

The current trends in the new multifocals (mf) IOLs presbyopic IOLs are diffractive and refractive models. The former have reached a high standard of clinical performance and are designed to eliminate halos and glare by decreasing the near optical power, according to Dr. Alio, professor and chairman of ophthalmology, VISSUM, Instituto Oftalmologico de Alicante, Universidad Miguel Hernandez, Alicante, Spain.

“The new models combine manipulation of aberrations with multifocality and are referred to as a new hybrid mfIOL,” he explained.

EXTENDED-DEPTH-OF-FOCUS (EDOF) IOLS

This is the most recent technologic advance to become available for treating presbyopia. According to Dr. Alio, these lenses manipulate the IOL’s spherical aberration (SA) so that the incoming light waves are elongated, which eliminates both the overlap of near and far images and the halos. These IOLs were designed to improve the intermediate vision. An associated limitation is the decreased retinal image quality, and for this reason the near vision add is limited to about 1 D.

A number of companies have investigated this approach. Dr. Alio mentioned the Wichterle IOL (Medicem), a continuous-focus model that manipulates SAs. The idea behind this single-piece polyfocal hyperbolic optic with no haptics was that it mimicked the natural young crystalline lens, with the possibility of accommodation; however, poor visual quality forced the company to abandon this model. The Mini Well monofocal IOL (SIL), another EDOF IOL, induces SAs in specific areas of the optic to increase the depth of focus and generate multifocality.

Another way of achieving the EDOF effect is use of the pinhole effect. The IC-8 (AcuFocus, Inc.), which uses a small aperture, achieves an extended and continuous range of vision using an embedded opaque annular mask of 1.36 mm that blocks unfocused paracentral light rays and permits paraxial light rays to enter. The XtraFocus Pinhole Implant (Morcher) is based on the same principle using a smaller pinhole of 1.3 mm.

The EDOF IOLs are approved only for distance and intermediate vision. Patients will need at least 1 D of correction for near vision. Postoperative patient dissatisfaction is attributed to intolerance of the total induced aberrations. If there is excessive EDOF, the quality of vision is affected. The explantation rate is higher.

HYBRID MODELS

The disadvantages of the EDOF IOLs led to the development of mfIOLs with an EDOF system. “The multifocality and EDOF characteristics are not exclusive of each other,” Dr. Alio noted.

The hybrids balance three interrelated factors: visual acuity, depth of field, and dysphotopsias. The increasing depth of field and decreasing multifocality are tempered to avoid the negative impact on the near vision. The Tecnis Symfony (Johnson & Johnson Vision) was the first such IOL with a 1.75-diopter near add. The AcrySof IQ panoptix (Alcon) is a mfIOL that adds a negative SA on the anterior surface to compensate for the positive SA of the human cornea.

NEW REFRACTIVE MFIOLS

The refractive IOLs offer new optical profiles, as seen in the Precizon Presbyopic (Ophtec), and new materials,
as exemplified by the Acunex Vario AN6V (Oculentis). The former IOL offers constant progressive focus between two focal points and no light loss. The latter IOL uses the previous optical technology of focal IOLs without a varifocal lens with new biometry that results in a different profile and prevents opacification; the IOL incorporates changes in SA and haptics and offers EDOF. “Some of the so-called EDOF IOLs available today are really mfiOLs with low power in which part of the rest of the power has been withdrawn to avoid the overlapping of images and the consequent halos and glare,” Dr. Alio explained. “IOLs should be referred to as EDOF only when they do not have either refractive or diffractive added multifocality. If so, they should be considered hybrid m/f/EDOF IOL.”

**OTHER OPTIONS**

The Care Group introduced the Presby IPCL, a trifocal diffractive optic that is implanted in the sulcus to treat patients with advanced presbyopia. Add-on piggyback mfiOLs are another option. The Sulcoflex (Rayner), a hydrophilic acrylic implanted in the sulcus. The results have shown that this IOL implanted atop a previously implanted monofocal IOL offers positive results. Other such IOLs include the Restor (Alcon), Trifocal (Zeiss), and Mplus (Oculentis). An important question that remains unanswered is whether accommodation can be restored by an IOL. The bottom line thus far is that IOLs have not provided accommodation and have failed to provide an alternative to monofocal IOLs. “The question remains about whether these IOLs should be placed inside or outside the capsular bag. Answering this question could determine the future of accommodative IOLs,” he said.

Dr. Alio and colleagues have investigated this problem in a primate model and determined that there is no accommodative force in the capsular bag related to ciliary body stimulation 6 months postoperatively, which demonstrated that the sulcus and not the bag is the place for an accommodative IOL. The Lumina (Akkolens), an sulcus-based accommodative IOL has so far produced good results. The results indicated that this IOL restored visual function, accommodation, and contrast sensitivity after cataract surgery with no affect on the contrast sensitivity, he reported.

**CONCLUSIONS**

Dr. Alio emphasized issues surrounding presbyopic IOLs. “Optical quality and retinal quality are essential elements of the performance of an IOL, but visual performance involves neuroprocessing and is a cortical perception,” he said. “How much of each is involved? To address this, we must define success.”

Dr. Alio explained that the most relevant factor is the quality of the retinal image. Study of the defocus curves has made it clear that EDOF IOLs are insufficient for near vision and good for far vision. He noted that new presbyopic IOLs represent opportunities for the present and future, and urged clinicians to choose their IOLs carefully using evidence-based information. “To use the EDOF, mfiOLs, and hybrids properly, we must be aware of what they offer and how they fit our patients’ needs,” he concluded. “There currently is confusion in terminology caused by an inappropriate commercial bias, leading to misinformation for practicing clinicians. Artificial intelligence IOLs are raising new expectations for near vision restoration in pseudophakia.”

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**References:**
Achieving successful results with refractive cataract surgery

Outcomes require understanding of patient needs, IOL performance characteristics

By Cheryl Guttman Krader; Reviewed by Florian Kretz, MD, FEBO

PATIENT SATISFACTION AFTER refractive cataract surgery depends on choosing an IOL that meets the individual's needs for uncorrected vision but also tolerance to dysphotopsias. According to Florian A. Kretz, MD, FEBO, approaches using rotationally asymmetric IOLs that do not have a diffractive optic design allow success for patients who are not willing to accept problems with glare and halos.

Dr. Kretz is medical director of Augentagesklinik Rheine and Greven, Germany. He discussed approaches using the Lentis-313 MF15 or MF20 IOLs (both from Oculentis) and the performance of these extended depth of focus implants.

“Choosing these approaches can result in very satisfied patients because the rotationally asymmetric IOLs provide high-quality vision and produce lower levels of dysphotopsias compared with diffractive presbyopia-correcting IOLs,” said Dr. Kretz.

MATCHING GOALS AND TECHNOLOGY

Dr. Kretz noted that cataract surgery patients interested in presbyopia correction can be grouped into three general categories based on their priorities for good uncorrected vision postoperatively. Some patients are near focused and have demands for excellent vision at reading distance (≤40 cm). Others seek good vision at all distances. The third group is described as distance-focused patients most interested in clear vision at the intermediate to far range, and are willing to wear glasses for reading.

The strategies for addressing these visual needs include binocular implantation of the Lentis-313 MF15 or MF20 IOL with a refractive target of emmetropia. These extended depth of focus IOLs provide a high degree of spectacle independence from distance to intermediate but also some functional reading vision.

“These IOLs are aberration neutral,” Dr. Kretz said. “Patients will use the spherical aberration of the cornea to enhance the depth of focus, which can improve their near vision.”

For patients with stronger near vision needs, surgeons can create blended vision using a micromonovision approach, implanting either the Lentis-313 MF15 or MF20 IOL bilaterally but targeting -1.25 D to -1.75 D in the non-dominant eye. Another solution for providing good reading ability is to implant the Lentis-313 MF15 or M20 in the distance dominant eye and a multifocal IOL (Lentis MF30 or Mplus X) in the fellow eye. Combining a pinhole lens (IC-8, Acufocus) in the near eye with the Lentis-313 MF15 of MF20 in the dominant eye can be a particularly good choice in patients who have irregular astigmatism.

“The pinhole hole can compensate for irregular astigmatism and is also not likely to cause dysphotopsias,” Dr. Kretz said.

CLINICAL PERFORMANCE

Outcomes data from testing of visual acuity, optical quality, defocus curves, and dysphotopsias provide evidence about the excellent clinical performance of the Lentis-313 MF15 and MF20 IOLs. Dr. Kretz reported visual acuity results showing that the Lentis-313 MF15 IOL delivers distance visual acuity that is comparable to a monofocal aberration neutral IOL (CT Asphina 409). Objective testing of optical quality (HD Analyzer, Visiometrics) also showed similarity between the presbyopia-correcting IOL and the monofocal lens.

Defocus curves from testing of patients implanted with some of the different approaches described by Dr. Kretz showed the wide range of good uncorrected vision achieved. Testing for dysphotopsias conducted using a halo and glare simulator showed no difference in the occurrence or severity of these dysphotopsias comparing patients implanted with the EDOF IOLs versus the monofocal lens.

“Remember that even patients with a monofocal IOL can have halo and glare because of the presence of spherical aberration and other higher-order aberrations in the cornea,” Dr. Kretz said.

“If you look preoperatively at patients who have cataracts, you will see that their problems with dysphotopsias are even worse before surgery.”

Halo and Glare Simulator Results

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<th>CT Asphina 409</th>
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Results of the halo and glare simulations comparing multifocal and monofocal IOLs. (Data courtesy of Florian Kretz, MD, FEBO)
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INDICATIONS: The TECNIS Symfony Extended Range of Vision IOL, Model ZXR00, is indicated for primary implantation for the visual correction of aphakia, in adult patients with less than 1 diopter of pre-existing corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The Model ZXR00 IOL is intended for capsular bag placement only. WARNINGS: Patients with any of the conditions described in the Directions for Use may not be suitable candidates for an intraocular lens because the lens may exacerbate an existing condition, may interfere with diagnosis or treatment of a condition, or may pose an unreasonable risk to the patient’s eyesight. Lenses should not be placed in the ciliary sulcus. May cause a reduction in contrast sensitivity under certain conditions, compared to an aspheric monofocal IOL, fully inform the patient of this risk before implanting the lens. Special consideration should be made in patients with macular disease, amblyopia, corneal irregularities, or other ocular disease. Inform patients to exercise special caution when driving at night or in poor visibility conditions. Some visual effects may be expected due to the lens design, including a perception of halos, glare, or starbursts around lights under nighttime conditions. These will be bothersome or very bothersome in some people, particularly in low-illumination conditions, and on rare occasions, may be significant enough that the patient may request removal of the IOL. SERIOUS ADVERSE EVENTS: The most frequently reported serious adverse events that occurred during the clinical trial of the TECNIS Symfony lens were cystoid macular edema (2 eyes, 0.7%) and surgical reintervention (treatment injections for cystoid macular edema and endophthalmitis, 2 eyes, 0.7%). No lens-related adverse events occurred during the trial.

TECNI5 MULTIFOCAL FAMILY OF 1-PIECE IOLs

INDICATIONS: The TECNIS Multifocal 1-Piece intraocular lenses are indicated for primary implantation for the visual correction of aphakia in adult patients with and without presbyopia in whom a cataractous lens has been removed by phacoemulsification and who desire near, intermediate, and distance vision with increased spectacle independence. The intraocular lenses are intended to be placed in the capsular bag. WARNINGS: Physicians considering lens implantation should weigh the potential risk/benefit ratio for any conditions described in the Directions for Use that could increase complications or impact patient outcomes. Multifocal IOL implants may be inadvisable in patients where central visual field reduction may not be tolerated, such as macular degeneration, retinal pigment epithelium changes, and glaucoma. The lens should not be placed in the ciliary sulcus. Inform patients about the possibility that a decrease in contrast sensitivity and an increase in visual disturbances may affect their ability to drive a car under certain environmental conditions, such as driving at night or in poor visibility conditions. PRECAUTIONS: Prior to surgery, inform prospective patients of the possible risks and benefits associated with the use of this device and provide a copy of the patient information brochure to the patient. Secondary glaucoma has been reported occasionally in patients with controlled glaucoma who received lens implants. ADVERSE EVENTS: The rates of surgical re-interventions, most of which were non-lens related, were statistically higher than the FDA grid rate for the ZLB00 (+3.25 D) lens model. The re-intervention rate was 3.3% for both the first and second eyes in the ZLB00 group.

ATTENTION: Reference the Directions for Use for a complete listing of Indications and Important Safety Information.


See the Passion in Each Patient
The future: Development of true accommodative IOLs

Researchers work on restoring accommodation, whether on cornea, lens or sclera

By Steve Lenier; Reviewed by Florence Cabot, MD

Like space in the “Star Trek” motion picture series, presbyopia remains one of the final frontiers of refractive surgery, but efforts are under way to develop the real restoration of accommodation.

Over the years, the results of accommodative pseudophakic IOLs have been mixed, but that may be ready to change and the last frontier of ophthalmology may be tamed with new lenses that provide options for surgeons and hope for their patients.

Accommodation and presbyopia involve several ocular structures—the ciliary muscle, pupil, lens, zonule, vitreous, and some brain structures and neural pathways as well. This makes restoring accommodation complex.

Restoring accommodation means creating a device that has a continuously variable, adjustable, active, near-focusing ability. This can be thought of as similar to the autofocus of a camera. Over the years, several teams have worked on restoring accommodation, whether on the cornea, the lens, or on the sclera.

**FIRST GENERATION IOLs**

The first generation of accommodative IOLs relied on the Helmholtz theory of accommodation. The lenses are supposed to provide a forward shift, because they have flexible haptics that should respond to the contraction of the ciliary muscle. Results have been disappointing, and the few good results that have been seen were attributed to an increase of optical aberrations rather than an actual movement of the lens.

The Ophthalmic Biophysics Center (OBC) at the Bascom Palmer Eye Institute in Miami, FL, built a unique dual OCT system that provides dynamic imaging, so real-time video of the ciliary muscle can be seen on one side, with the anterior segment seen on the other side.

Researchers used that system to image patients that had received a Crystalens (Bausch + Lomb), a first-generation accommodative lens. They could see that after a 2 D accommodation stimulus the Crystalens was actually showing either a minimal forward axial shift (not able to provide useful accommodation to the patient), or no axial shift at all, or a backward axial shift in some cases.

**MODULAR AND MULTICOMPONENT IOLs**

The new-generation accommodative IOLs are modular and multicomponent, and provide postoperative adjustability. In both categories, the exact effective lens position is known. This allows precise IOL calculations and refractive outcomes.

**MULTICOMPONENT OPEN CAPSULE IOLs**

Some lenses do not have continuous adjustability, but allow for an adjustment to be made after the operation, and repeated over time. Within this category there are two subcategories. The first consists of two parts, a base component and an optic component. The Gemini Capsule from Omega Ophthalmics, the Harmoni from ClarVista Medical, and the Precisight from infiniteVision Optics are this type of lens. These keep the capsule open, thus preventing posterior capsular opacification. The haptics stay in the bag while the optics can be exchanged and adjusted as many times as necessary later on.

In this video still, a patient has a Crystalens implant that does not move forward. (Photo courtesy of Florence Cabot, MD)
Understanding expanding role of IPL in dry eye disease

Signs of inflammation, meibomian gland dysfunction indicate treatment may be required

By Richard Adler, MD; Special to Ophthalmology Times

INFLAMMATION IS WIDELY understood to be an integral component in chronic dry eye disease (DED). More than two decades of research has helped elucidate the role of inflammation in instigating and perpetuating chronic dry eye. It is now considered an accepted fact that chronic dry eye is a cyclical inflammatory process: Even short-term desiccating stress at the ocular surface increases osmolarity, causing an outflux of intracellular fluid, and thereby yielding cell shrinkage that leads to the release of inflammatory mediators (such as interleukin-6 and -8).

These mediators further decrease tear production while increasing osmolarity—which then re-starts the cycle that culminates in hallmark symptoms of ocular surface discomfort and fluctuating visual acuity.1 Meanwhile, a host of pro-inflammatory cytokines, chemokines, and their receptors have been implicated in playing a central role in disease progression.1 It seems that inflammatory processes are also relevant in the earliest stages: the prevailing theory at the current time regarding the initial cause of dry eye is that dysregulated immune system responses—in reaction to environmental or physiologic stressors—initiate and sustain the abnormal inflammatory cycle inherent to dry eye.1

What those of us who manage patients with dry eye can take away from all of this is that inflammation plays a key role in initiating, perpetuating, and causing dry eye progression. As a result, if ophthalmologists are not treating

Continues on page 22: IPL

IOLS

(Continued from page 20)

MODULAR IOLS
The other subcategory is a single component lens, with the adjustability achieved through a reshaping of the IOL itself, which is done with UV light or a femtosecond laser. This category includes the Light Adjustable Lens (LAL) from RxSight (adjustment done with UV light a few weeks after surgery), and the femtosecond laser-adjustable system from Perfect Lens, which can be used to reshape any acrylic IOL.

ACCOMMODATIVE IOLS WITH INSTANTANEOUS, CONSTANT ADJUSTABILITY
These lenses rely on ciliary muscle movements or pupillary changes to provide a real time change in their shape to provide near vision. There are two subcategories here, IOLs that are injected into the bag, and IOLs that are implanted in the sulcus or fixated to the sclera. The main reason for implanting outside of the bag is to avoid capsular bag fibrosis.

IN-THE-BAG IOLS
The Synchrony lens from Visiogen, the WIOL-CF from Medicem, and one of the newest, the Juvene by LensGen, are in this group.

Another interesting concept, just at the experimental level with Sapphire’s Elenza, is injecting a chip into the capsular bag, which has a sensor. A change in pupil size can trigger an automatic adjustment exactly like auto focus, and there can also be a remote control used to change the accommodation. Looking further, this could be integrated with artificial intelligence to become even more useful.

OUT-OF-THE-BAG IOLS
The NuLens Dynacurve uses the collapsed bag – zonular complex as a diaphragm, which drives a piston system that changes the shape of the lens, and the AkkoLens Lumina is injected into the sulcus and has two optics that slide perpendicular to the visual axis in response to the ciliary muscle for near focus.

ACCOMMODATING FLUIDS/LENS REFILLING TECHNOLOGY
This technology is utilized by the Nishi Lens Refilling IOL, the Phaco-Ersatz from Ophthalmic Biophysics Center at the Bascom Palmer Eye Institute, the Smart IOL by Medennium, and the Liquilens by Vision Solutions. Despite years of development, it is still difficult to get good results with this type of technology.

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Dr. Cabot has no relevant financial interests to disclose.

A Crystalens IOL is injected into the eye of a patient. (Photo courtesy of Florence Cabot, MD)
IPL

(Continued from page 21)

the inflammation, we are not treating this disease.

WHY IPL MAKES SENSE

The classic thinking by physicians centered around the use of intense pulsed light (IPL) in treating dry eye is that active signs of inflammation (such as facial and/or ocular rosacea and telangiectasia) or meibomian gland dysfunction (MGD) indicate the treatment might be successful.

IPL

As an additional note, IPL treatment also indirectly interrupts the dry eye inflammation cycle by reducing the osmolarity of the tear film to normal levels.

TECHNOLOGY

I have been using IPL with my dry eye patients since around 2010. I currently use the Optima IPL (Lumenis).

Over the past decade, clinical studies have demonstrated the effectiveness of Lumenis’ IPL platforms for treating DED.5 11

In my view, using Lumenis IPL technology has several advantages:

First, the company has been in the space for decades. There are no click fees or disposables associated with performing the treatment.

For those interested in using IPL in applications outside of eye care—including medical aesthetic—

The Optima IPL is part of the modular aesthetic laser multi-application platform (M22), which allows a user to select and use different wavelengths of light.

With regard to the Optima IPL, specifically, the platform permits higher energy levels for effective treatment of inflammation while maintaining patient comfort and in a unique cooling system. Individual pulses have higher energy as well.

A 10 J/cm² setting is three pulses of 3.33 J/cm², rather than five 2 J/cm² pulses, as with other systems. The energy can also be lowered to treat fragile or sensitive skin, and is compatible with a wide range of tip sizes that allow ease of access around the tricky periorcular anatomy.

Some of the features noted above speak to the broad applications of IPL in treating skin on the face and around the eye, as well as for treating the ocular surface.

As an additional note, IPL treatment also indirectly interrupts the dry eye inflammation cycle by reducing the osmolarity of the tear film to normal levels.7 8

The fundamental reason IPL is successful for dry eye is that it treats the upstream inflammatory root cause of DED—not just the downstream consequences, as its multiple mechanisms of action collectively interrupt the vicious inflammatory cycle that instigates and perpetuates dry eye.

It is an effective standalone procedure for patients suffering with aqueous deficient, evaporative, or mixed modal etiology dry eye.

IPL can also easily be added to pharmacology or other device-based treatments in a multimodality approach to treating the multifactorial entity of DED.

‘IPL can also easily be added to pharmacology or other device-based treatments in a multimodality approach to treating the multifactorial entity of DED.’

— Richard Adler, MD

CHOOSING PATIENTS

But even within the category of ocular surface disease (OSD), there is wide range of patients for whom IPL makes sense. Generally speaking, patients who have tried traditional therapies and are still struggling may get relief from their dry eye symptoms with IPL.

On the other end of the spectrum, I have found that many newly diagnosed patients simply do not want to use pharmacotherapy, and so a device-based treatment offers a different yet equally effective approach.

Of course, there are myriad opportunities in between those two extremes.

REFERENCES


TAKE-HOME

» The fundamental reason IPL is successful for dry eye is that it treats the upstream inflammatory root cause of DED—not just the downstream consequences, as its multiple mechanisms of action collectively interrupt the vicious inflammatory cycle that instigates and perpetuates dry eye.

■■ Richard Adler, MD

Dr. Adler is based in Baltimore, and is a corneal specialist at Belcara Health. He did not indicate a proprietary interest.
Striving for perfection: Creating the ideal IOL

Several attributes go into formulating the lens of the future

By Cheryl Guttman Krader; Reviewed by Gerd U. Auffarth, MD, PhD

UNDERSTANDING THE CHARACTERISTICS of available IOL materials provides insight for developing a perfect IOL for the future, according to Gerd U. Auffarth, MD, PhD. According to Dr. Auffarth’s review of this topic, the perfect material would be optically pure without risk for calcification, glistenings, interaction with substances inside the eye, or long-term degeneration. Dr. Auffarth is chairman, Department of Ophthalmology, Ruprecht-Karls-University of Heidelberg, Heidelberg, Germany.

Consideration would be given to refractive index, which dictates material thickness and therefore surgical incision size. Other issues include Abbe number and optical features of the material that are related to refraction and potential side effects, as well as the opportunity for changeability.

Data on the IOL global market show dominance of acrylic lenses, with hydrophobic acrylic IOLs accounting for 56% of implants worldwide and hydrophilic acrylics having a 29% market share overall.

Discussing the properties of the two types of acrylics, Dr. Auffarth explained that the hydrophobic materials are copolymers that are related to polymethylmethacrylate. The various hydrophobic acrylics are relatively similar with respect to refractive index, which is approximately 1.5 (range 1.41 to 1.55), he said.

“High-refractive index is one of the advantages of hydrophobic acrylic as an IOL material,” Dr. Auffarth added. “Other advantages include a low rate of posterior capsule opacification (PCO), rotational stability, resistance against both capsular contraction and Nd:YAG laser-induced damage, and freedom from calcification because the material is inert.”

Hydrophobic acrylic IOLs have limitations. An association with negative dysphotopsias is one disadvantage cited for hydrophobic acrylic lenses.

“Reports of negative dysphotopsias with IOLs are mostly limited to individual cases or cases series,” Dr. Auffarth said. “Although hydrophobic acrylic lenses are often involved, they have the highest market share.”

The potential for mechanical damage and glistenings is an issue with hydrophobic acrylic materials. Glistenings, which are fluid-filled microvacuoles within the polymer network, can be present before implantation or develop over time when the lens is in the eye.

“Glistenings are not just a cosmetic issue, because they can have a clinical impact by increasing straylight,” Dr. Auffarth pointed out. “With the use of an experimental model for accelerating glistening formation, however, we have found that manufacturers are now doing a good job producing glistening-free lenses.”

Hydrophilic acrylate IOLs are mostly made of polyhydroxyethyleneacrylate and other copolymers. Their advantages include foldability and high biocompatibility. Their high-water content, however, is a disadvantage because it leads to a risk for calcification when the material is in the aqueous environment within the eye or exposed to air or gas, which can occur during various surgical procedures.

Although it can be difficult to get information from manufacturers about IOL materials in development, through collaboration with a Chinese company (Pillarbio), Dr. Auffarth described features of a novel IOL material that is a crosslinked polyisobutylene.

The material also has a high refractive index (1.52) and high Abbe number (50), stable physicochemical properties, low modulus, high elasticity, and superb long-term clarity.

“This material appears to resolve current concerns regarding glistenings, dysphotopsias, chronic inflammation, and PCO. The high-refractive index and Abbe number also allow for a large optic that would enable retina observation,” said Dr. Auffarth.

TAKE-HOME

- With acrylic lenses currently dominating the market, the industry continues to consider viable options for IOL materials.

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This article is based on a presentation given by Dr. Auffarth at the 37th Congress of the European Society of Cataract and Refractive Surgeons. Dr. Auffarth receives research grants from many companies that manufacture IOLs.

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Liquid biopsies: Not yet ready for prime time?

Technique currently unreliable to predict prognosis in uveal melanoma

By Lynda Charters; Reviewed by Martine J. Jager, MD, PhD, and Annemijn P.A. Wierenga, MD

Quickly obtaining a sample of aqueous fluid for biopsy in intraocular malignancies would be a remarkable advance instead of having to rely on a biopsy of tumor tissue. As in uveitis, it could be done in an outpatient setting.

This approach, if available, would be extremely useful for a number of purposes, according to Martine J. Jager, MD, PhD, professor of ophthalmology, Leiden University Medical Center, Leiden, The Netherlands.

“A liquid biopsy from the eye or blood could be used for diagnostic purposes, prognosis, follow-up and early detection of metastases, and treatment. Clinicians could evaluate many different factors, including cells, proteins, messenger RNA [mRNA], and DNA,” she said.

A recent example of what can be achieved comes from retinoblastoma. Now that an intraocular injection of chemotherapy into eyes with retinoblastoma is an accepted clinical procedure in selected eyes, physicians can also study the presence of tumor material in the blood obtained from these eyes.

Jesse Berry, MD, associate professor of ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, compared chromosome changes in the aqueous of eyes with retinoblastoma with tumor material and found excellent correspondence (JAMA Ophthalmol. 2017; 135:1221-1230). However, further research is needed to delineate the role of this test in retinoblastoma.

Investigators have similarly been attempting using liquid biopsies for uveal melanoma.

Dr. Jager described a study in which a group of French authors investigated the detection rate and prognostic value of circulating tumor cells (CTCs) and circulating tumor (ct) DNA by evaluating the presence of DNA with a GNAO or GNA11 mutation in the blood of patients with metastatic uveal melanoma (Int J Cancer 2014;134:1207-1213). This study of 40 patients reported that 12 patients had CTCs in the blood and 18 of 22 testable patients had ctDNA with a mutation in the blood. The study results showed, according to Dr. Jager, that even patients with a large load of metastases do not always have CTCs in the blood or DNA, but that the presence of CTCs and ctDNA predicted a worse progression-free survival.

mRNA also was used to test for the presence of RNA for pigment cell markers (MelanA or MART1) (Oncology. 2011;80:57-62). The results similarly indicated that even when primary uveal melanoma had metastasized, circulating-tumor cell specific mRNA was often not present in the blood, indicating that this test was not a good prognosticator.

Another study evaluated circulating melanoma cells by dual-marker immunoenrichment in which positive cells were selected from the blood (Invest Ophthalmol Vis Sci. 2014;55:4395-4404) using the FISH technique to screen for chromosome 3 status. The authors reported that at the time of enucleation, CTCs were detected in the blood of 29 of 31 patients with uveal melanoma.

In a follow-up study, a correlation was shown between chromosome 3 status in the circulating melanoma cells and the primary tumor (Pigment Cell Mel Res. 2016;29:583-589).

The studies described concluded that all tests detected some tumor cell material in the blood, but not one of the tests was considered good for predicting prognosis. Especially the inability to detect tumor cell-derived material in the blood is not a guarantee of a good prognosis. Even the presence of large tumors did not yield results in many patients, Dr. Jager said.

The presence of interleukins in the blood is already known to be a valuable marker in patients with intraocular lymphoma. Dr. Jager explained that a poor prognosis (monosomy 3/class 2) is associated with inflammation of primary uveal melanoma. Numerous T cells and macrophages were specifically found in the tumors of patients with monosomy 3; when chromosome 3 was normal, few macrophages were found. (Invest Ophthalmol Vis Sci. 2012;53:5370-5378). Based on this, she and her colleague Annemijn P.A. Wierenga, MD, who is a clinical research fellow at Leiden University Medical Center, looked for inflammatory cytokines in relatively large tumors in enucleated eyes.

The question in this study was whether the prognosis was predictable by analyzing aqueous humor samples based on the presence or absence of inflammation. In previous studies that evaluated this issue, eyes with uveal melanoma had more cytokines in the aqueous than eyes with...

LOOKING AT INTERLEUKINS

The presence of interleukins in the blood is already known to be a valuable marker in patients with intraocular lymphoma. Dr. Jager explained that a poor prognosis (monosomy 3/class 2) is associated with inflammation of primary uveal melanoma. Numerous T cells and macrophages were specifically found in the tumors of patients with monosomy 3; when chromosome 3 was normal, few macrophages were found. (Invest Ophthalmol Vis Sci. 2012;53:5370-5378). Based on this, she and her colleague Annemijn P.A. Wierenga, MD, who is a clinical research fellow at Leiden University Medical Center, looked for inflammatory cytokines in relatively large tumors in enucleated eyes.

The question in this study was whether the prognosis was predictable by analyzing aqueous humor samples based on the presence or absence of inflammation. In previous studies that...
nevi, some cytokines in aqueous were correlated with ciliary body involvement, and in the vitreous fluid cytokines were related to immune cell infiltration (Invest Ophthalmol Vis Sci. 2012;53:6748-6755). However, it remained unknown if the level of inflammation in the aqueous humor represented monosomy 3/class 2, Dr. Jager explained.

In Dr. Wierenga’s recent study, 90 samples from enucleated eyes with known chromosome status were evaluated using a multiplex immunoassay.

“Clustering analysis indicated that there were three distinct groups: cluster 3, those positive for almost every cytokine analyzed, cluster 2, those with intermediate responses, and cluster 1, those with negative responses,” she noted. “Many eyes with uveal melanoma have absolutely no cytokines in the fluid in the anterior chamber that can be detected by this test.”

When the investigators compared the survival rates of the three groups, they found that patients with low cytokine levels (negative responses) had a better survival compared to patients in clusters 2 and 3 (p = 0.02 and p = 0.004, respectively). Clusters 2 and 3 did not differ significantly from each other.

“Are the results related to the tumor status? Large tumors clearly had more cytokines,” Dr. Jager noted. “Tumors with monosomy 3 were present in nine of 10 patients in cluster 3; however, patients in the other clusters also had monosomy 3. We are now comparing individual markers with clinical status and progression, but this test is not yet clinically applicable.”

Dr. Jager added that liquid biopsies of blood, aqueous humor, or vitreous fluid cannot currently reliably predict prognosis either at the time of uveal melanoma treatment or treatment of metastases.

“False-negative results especially affect the tests. Sampling of intraocular fluid may indicate an inflammatory phenotype. Developing new tests based on eye fluid or blood would be a wonderful accomplishment,” she concluded.

‘Many eyes with uveal melanoma have absolutely no cytokines in the fluid in the anterior chamber that can be detected by this test.’

— Annemijn P.A. Wierenga, MD,
Microscopy study suggests stem cell success in keratoconus

ADAScs injected into the stromal pocket of patients with keratoconus can transform into keratocytes, according to Mona El Zarif, OD, Msc.

**By Laird Harrison; Reviewed by Mona El Zarif, OD, Msc**

New evidence with confocal microscopy shows that adipose-derived adult stem cells (ADAScs) injected into the stromal pocket of patients with keratoconus can transform into keratocytes, according to Mona El Zarif, OD, Msc.

The use of confocal microscopy to monitor and evaluate the evolution of the stem cells over time is novel, said Dr. El Zarif, a doctoral student at Miguel Hernández University in Alicante, Spain, at the European Society of Cataract and Refractive Surgeons (ESCRS) annual meeting.

“It allowed a qualitative and quantitative assessment of the cells,” she explained.

The technique establishes a new methodology to count the keratocytes in the corneal stroma, and measure the density of the ADAScs in the implanted tissue, as well as the corneal stroma she said.

**THREE GROUPS**

The researchers compared three groups of adult patients with keratoconus in an experimental, interventional, prospective, consecutive case series. In the first group, five patients were implanted with ADAScs alone without scaffold.

In the second group, five patients were implanted with decellularized human corneal stroma, essentially a scaffold without ADAScs.

“We decellularize the lamina from the donor human cornea stroma,” Dr. El Zarif noted.

**ADASCS USED**

The third group was implanted with ADAScs embedded onto a scaffold made from a decellularized lamina.

“We observed that the automatic count of cells done by the software of the confocal microscopy was not accurate,” said Dr. El Zarif. “That’s why we proceeded with a manual count of cells. We proceeded choosing a good image, a good number of keratocytes and good contrast and quality of illumination.”

For anyone wanting to try this approach, she recommends starting the count of cells with 50% illumination and contrast determining a fixed area.

In this study, Dr. El Zarif analyzed an area of about 0.1 mm and counted the most illuminated and most refringent cells with well-defined edges.

“The dark gray cells are not counted in our study because they don’t belong to the plan of observation,” she said.

When the researchers could not find any defined structure similar to keratocytes, they considered the tissue in question to be acellular.

By this definition, the decellularized lamina in this study remained acellular a month after implantation.

By contrast, cells in the recellularized lamina after one month had structures similar to normal keratocytes. And these cells became more similar to keratocytes six to 12 months postoperation.

The researchers used software in the confocal microscope to calculate the density of the cells. They defined cell density as the number of cells multiplied by 10 (cell/mm²) ±/− SD.

The results were promising. In the first group, those implanted with ADAScs but no scaffold, the ADASc appeared round in shape, and more luminous, refringent, and voluminous. The shape of ADASc changed after 6 months from round to fusiform until after 12 months the morphology of these cells looked like a normal cornea.

In the second group, those patients implanted with decellularized lamina only, the lamina remained acellular for the first month after implantation.

**RECELLULARIZED**

After three months, it became recellularized by the patients’ own keratocytes.

“There was a migration of keratocytes from the host stroma toward the lamina,” said Dr. Zarif. The posterior surface of the lamina recellularized before the anterior surface. After a year, the keratocytes populated the lamina in a similar way to a normal cornea stroma.

The third group, implanted with recellularized lamina, showed structures like normal keratocytes after one month. These were more voluminous in the posterior surface of the lamina. With some patients they had dendritic shape after one year of implantation.

The results were promising. In the first group, those implanted with ADAScs but no scaffold, the ADASc appeared round in shape, and more luminous, refringent, and voluminous. The shape of ADASc changed after 6 months from round to fusiform until after 12 months the morphology of these cells looked like a normal cornea.

In the second group, those patients implanted with decellularized lamina only, the lamina remained acellular for the first month after implantation.

**TAKE-HOME**

» The use of confocal microscopy establishes a new methodology to count the keratocytes in the corneal stroma, and measure the density of the ADAScs in the implanted tissue, as well in the corneal stroma.
Biomarkers are defined by the FDA as characteristics of every facet of a disease, i.e., the bacteria, molecules in the diagnosis and prognostication of diseases. "It is most important to understand the behavior of every facet of a disease, i.e., the bacteria, molecules in the diagnosis and prognostication of diseases."said Rohit Shetty, DNB, FRCS, PhD. "Even when considering the stem cells and scenarios the body faced decades previously, everything in the bodily system is changing." Dr. Shetty is a faculty member, Department of Ophthalmology, Maastricht University, Maastricht, The Netherlands, and vice chairman, Narayana Nethralaya Eye Institute, Bangalore, India.

In line with this perspective, another point for consideration is that the ophthalmologists can no longer be concerned with only what is happening in the eye. And the changing scenarios regarding food, exercise, and the gut microbiome are big challenges from a clinical perspective.

**BIOMARKERS AND OPHTHALMOLOGY**

A biomarker is defined by the FDA as a characteristic, that is measured as an indicator of normal biological and pathogenic processes or responses to an exposure or intervention, including therapeutic interventions. Applying this knowledge in clinical practice is most beneficial for clinicians.

According to Dr. Shetty, there is a great need for biomarkers in clinical practice in numerous areas, such as in the differential diagnosis, risk quantification, prognosis, and disease identification.

"The clinical signs and symptoms, imaging, and medical history may no longer be adequate," he said, noting that clinical scenarios such as identifying the predisposition to postoperative complications before refractive surgery and disease progression status, for example, in determining keratoconus stability and unilaterality or asymmetry in the clinical presentation.

"This finding provided the insight that we should start looking forward for progression status identification," Dr. Shetty explained. "And it allowed monitoring of the process itself," Dr. Shetty explained. For example, regarding keratoconus, the first question asked about the disease was whether it was an inflammatory or inflammatory disorder. Dr. Shetty’s work to address this question started with tear cytokine/chemokine profiling, which lead him to the observation of extensive inflammation in the epithelium and tears of keratoconus patients.

"This finding provided the insight that we should start looking forward for progression status indicator biomarkers in keratoconus," he said. "Tear collection at each visit allowed him and his research team to make new discoveries in each of the groups.

**MID CORNEAL STROMA**

As the study progressed, the research team continued to make new discoveries in each of the groups.

In the first group, the researchers noted a gradual but significant increase of the cellularity of the mid corneal stroma (p < 0.001).

In groups 2 and 3, one year after surgery, the researchers observed a significant increase (p < 0.001) in cellularity in the anterior and posterior surfaces and within the lamina.

**REVIEW HELPS RESEARCHERS FIND BIOMARKERS, REASONS, CAUSE, TREATMENT OPTIONS**

**HUMAN TEARS HOLD MANY SECRETS AND CLUES THAT CURRENTLY ARE BEING UNEARTHED TO AID PHYSICIANS IN THE DIAGNOSIS AND PROGNOSTICATION OF DISEASES.**

**STEM CELL**

(Continued from page 26)

In all three groups, 12 months after the surgery, the researchers noted gradual and significant increase in the cellularity of the anterior and posterior stromas of the patients in comparison to the preoperative density, with a p value for this difference of less than 0.001 in the anterior and posterior stroma.

**CELL DENSITY**

They found that cell density was significantly higher in patients implanted with recellularized laminas than in those implanted with decellularized laminas, both in the anterior surface and within the lamina (p = 0.011), and on the posterior surface of the lamina (p = 0.029).

After making its initial findings on cell density, the research team continued to follow up on this measurement.

After one year, group 3 had greater cell density than either group 2 or group 1 in the anterior stroma. It had greater cell density than group 2 in the anterior stroma, the anterior surface of the lamina, the mid stroma of the lamina and the posterior surface of the lamina.

**CONCLUSION**

In conclusion, Dr. El Zarif said, confocal microscopy is an essential tool for the evaluation and monitoring “in vivo” of the ADASC.

"It allowed a qualitative and quantitative assessment of the cells through the experiment," she said. "And it allowed monitoring of the progressive morphological changes that occurred in the implanted tissue in decellularized and recellularized laminas."

Dr. El Zarif added that the technique assisted in determining the change in the cells’ densities in the grafted tissue as well as in all the posterior and anterior corneal stroma.
team to identify changes in the tears that indicated progression or stabilization of the disease, such as increased matrix metalloproteinase (MMPs).

‘Eventually, we saw that some patients were progressing and others were not. We found significant and distinct differences between those who were and were not.’

— Rohit Shetty, DNB, FRCS, PhD

“The LOX was completely different in the cone from the periphery, the latter of which appeared normal,” he reported. Dr. Shetty explained that higher LOX levels in the cone epithelium correlated significantly with the optimal outcome after cross-linking. The lower LOX levels indicated that the cross-linking would not be as optimal as with higher levels.

LOX was a very important biomarker in cross-linking and in progression,” he stated. Dr. Shetty also reported a case of ectasia that developed after a SMILE procedure caused by LOX deficiency. Based on this case, his laboratory is working on developing an enzyme-based detection chip that would enable detection of such deficiencies in the patient’s tear preoperatively. He said he is hopeful that the prototype will be ready next year.


Reading the signature is the first important step. Dr. Shetty demonstrated epithelial cells with and without stress and the marked changes in the epithelial pattern, which drives keratoconus and dry eye.

The cell shape of stressed cells was severely altered, the intracellular organelles were unclear, and the cell-to-cell transport and interactions were compromised. “A major factor in oxidative stress is autophagy,” he explained. “Oxidative stress induces dysregulated autophagy in the corneal epithelium of keratoconus patients. Changes in autophagy drives a disease.”

In his investigation, Dr. Shetty further discovered that a commercially available lubricant containing trehalose augmented autophagy to ease the stress-induced inflammation in human corneal cells.

“The same biomarkers of autophagy can be changed to start functioning better,” he explained. Another area of investigation, the gut-eye axis demonstrates the emerging roles of the microbiome in ocular immunity and diseases. Microbiome profiling of lead Dr. Shetty to the discovery that the bacteria may be linked to keratoconus or dry eye.

C H I N A L A P P L I C A T I O N

A problem that has received extensive investigation is haze development after refractive surgery. After identifying a number of unique markers in patients who develop haze, Dr. Shetty carried his experiment a step further by to prove that alterations in molecules like PREX1 and TGFb were actually causing haze.

Dr. Shetty’s team found that overexpression of these two biomarkers causes increased fibrosis-associated factors and knockdown of the two resulted in decreased fibrosis-associated factors.

This field of investigation also involves the brain, which, according to Dr. Shetty, controls more than what is known. Investigators currently are examining biomarkers in the brain and the role of inflammation in depression.

“We are on a long journey that involves multiple steps from collecting samples to identifying biomarkers to developing a point-of-care kit to determine the root cause of the disorder,” Dr. Shetty concluded.

ROHIT SHETTY, DNB, FRCS, PhD
E: drrohitshetty@yahoo.com
Dr. Shetty received research grants from Alcon Surgical, Allergan, Microvision J&J, and Carl Zeiss.

in case you missed it

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Study: Intravitreal bevacizumab in diabetic patients limits macular edema after cataract surgery

AAO 2019: Encouraging results revealed from early trial of subretinal gene therapy for wet AMD
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B

iweekly anti-VEGF dosing is a potential option for treating neovascular age-related macular degeneration (nAMD) that is refractory to chronic monthly injections, according to Eric W. Schneider, MD.

Dr. Schneider’s statement was based on a retrospective case series of 18 patients that found significant reduction in refractory intraretinal and subretinal fluid along with improvement in visual acuity after receipt of five biweekly doses. The gains achieved with biweekly dosing were reduced but not completely eliminated after patients returned to standard of care monthly dosing. No serious ocular or systemic safety events were noted during the study period.

“Our ability to make any definitive conclusions about the safety and efficacy of biweekly dosing to treat refractory nAMD is limited by the study design. It is a small, retrospective analysis utilizing various combinations of different anti-VEGF agents and biweekly dosing regimens,” said Dr. Schneider, private practice, Tennessee Retina, Nashville, TN.

“The results are encouraging, however, and have led us to initiate a prospective study (TRISTAR) investigating biweekly aflibercept (Eylea, Regeneron) in a similarly refractory patient population,” he added. “The study is currently fully enrolled with 22 patients with the last patient’s last visit expected in November.”

Dr. Schneider noted that the study was an outgrowth of frustration with his inability to completely dry the macula in a subset of patients with nAMD. Despite aggressive monthly anti-VEGF therapy, persistent intraretinal and subretinal fluid remains a common challenge in treating patients with nAMD.

“We see evidence of this in our real-world clinical practices as well as in major clinical trials with all of the available anti-VEGF agents,” he said.

Dr. Schneider pointed out that there are limited options to escalate therapy in this refractory population.

“One approach is to increase the monthly dose of the anti-VEGF agent,” he explained. “This has been looked at in prospective fashion in several trials with mixed results. A second approach is to increase the frequency of dosing, an approach for which there is limited data available in the literature.”

For the current study, patients were identified through a billing record search for those diagnosed with exudative AMD having more than 10 claims for intravitreal injections over a 12-month period. The study included only patients with refractory nAMD receiving at least five consecutive biweekly (12-21 days) anti-VEGF injections with two week follow-up visits after the fifth biweekly injection, and a minimum of 12 months of follow-up after starting biweekly therapy. For purposes of the study, refractory disease was defined as persistent intra-/subretinal fluid on spectral domain OCT after at least six consecutive monthly (28 to 35 days) anti-VEGF injections.

The primary outcome looked at changes in best-corrected visual acuity (BCVA) and multiple OCT-based anatomic metrics from baseline to the sixth visit, which was two weeks after the fifth biweekly injection. Secondary endpoints evaluated changes when patients had their final biweekly visit and their first standard of care visit, which was defined as the first visit at least four weeks after a prior injection.

The 18 patients who were included in the study had received standard anti-VEGF dosing for a mean of 35.4 months prior to beginning biweekly treat.
Can glaucoma patients benefit from cell therapy approach?

Sustained delivery, other treatment options may change landscape

By Louise Gagnon

THE FUTURE OF glaucoma will likely not resemble the current state of management of the disease, with numerous advances on the horizon, according to Harry Quigley MD, the A. Edward Maumenee Professor of Ophthalmology at Johns Hopkins School of Medicine, Baltimore, MD.

Delivering the Bryan St. L. Liddy Lecture on the topic of the future of glaucoma therapy during the annual Sally Letson Symposium, Dr. Quigley stressed that patients are looking for treatments other than daily administration of eye drops.

“If I quit my career without having gotten rid of eye drops, then I will have failed,” Dr. Quigley told symposium attendees. “We need sustained delivery in some form, so patients do not have to remember to take something everyday. Sustained delivery of IOP drugs will get around a lot of problems.”

One of the advantages of sustained delivery is that patients, according to published research, which showed that glaucoma patients would consider these alternatives to daily eye drops if they avoided the need for surgery or showed superior efficacy over eye drops. (J Glaucoma. 2018 Apr;27(4):328-335.)

PATIENT ADHERENCE Glaucoma patients have been largely left on their own to stick to a daily regimen of using eye drops. Some technology innovations have looked at trying to increase adherence. These include cell phone robo-calls or texts, noted Dr. Quigley.

In one study, individuals randomly selected to receive reminders were more adherent to their therapy than those who were not. They increased adherence from 53% to 64% (P < .05). However, there was no statistical change amongst the 32 participants in the control group. JAMA Ophthalmol. 2014 Jul;132(7):845-50.

Another innovation is the Kali Drop device, a wireless monitoring device that provides accurate adherence monitoring, uses telephone feedback, and sends data to an ophthalmologist’s office in real time.

“It will pop up on your screen if they (patients) have not touched their drops,” said Dr. Quigley.

IDENTIFYING PROGRESSION Identifying patients who will experience catastrophic worsening, and ruling out those who will not, can be done by modifying the frequency with which visual field tests are conducted, according to Dr. Quigley.

“They represent under 10% of all patients, but we need to identify them as rapidly as we can,” Dr. Quigley explained.

Conducting an annual visual field test is not sufficient to identify patients who will have rapid progression of disease, underlined Dr. Quigley.

“If you will do a (visual) field test a year, it will take you four or five years to detect the patient is worsening, and if they are one of these catastrophic worsening people, by then, the horse is already out of the barn,” he said.

Dr. Quigley routinely performs five field tests in the first 18 months with a new patient, as well as measuring IOP before initiating medical therapy, in order to detect patients with and without fast disease progression, resuming a schedule of quarterly visits. (Ophthal. 2018 Apr;27(4):328-335.)

TAKE-HOME » Sustained delivery is needed to ensure that patients do not have to remember to take their medication every day.

STUDY (Continued from page 30)

‘One approach is to increase the monthly dose of the anti-VEGF agent.’

— Eric W. Schneider, MD

and aflibercept; only 5.6% had received standard dosing with bevacizumab monotherapy.

Mean Snellen BCVA at baseline was 20/82, mean central foveal thickness was 333.6 μm, 28% of patients had intraretinal fluid, and subretinal fluid was present in 89% of eyes.

The mean number of biweekly injections for the group was 18.1 and the treatments were given at a mean interval of 16.5 days.

A single patient (5%) received treatment with a single anti-VEGF agent whereas the rest received various combinations of ranibizumab (Lucentis, Genentech), aflibercept, and bevacizumab (Avastin, Genentech).

The analysis of anatomic outcomes showed statistically significant improvement in central subfield thickness (CST) and cube volume at the primary outcome visit and at the final biweekly visit. The improvement in CST was not sustained at the first standard of care visit.

“The analysis of anatomic outcomes showed statistically significant improvement in central subfield thickness (CST) and cube volume at the primary outcome visit and at the final biweekly visit. The improvement in CST was not sustained at the first standard of care visit.

Mean Snellen BCVA improved by 13.7 letters, and CST was improved by 29.3 μm.

“One approach is to increase the monthly dose of the anti-VEGF agent.”

— Eric W. Schneider, MD

“About 35% of patients achieved complete resolution of subretinal fluid during biweekly dosing, although this effect waned somewhat upon return to standard of care dosing and the impact of biweekly dosing on the resolution of intraretinal fluid was less notable,” Dr. Schneider reported.

Visual acuity also improved significantly at the primary outcome visit (sixth visit), reaching a mean of 20/51, but it worsened to 20/65 at the final biweekly visit and was 20/67 at the first standard of care visit.

About 70% of patients maintained or gained vision and the majority gained at least one line of vision at all three assessments.
The ABCs of VEGF treatment for diabetic macular edema

SWAP-TWO study shows anatomic improvement after switch to aflibercept

By Michelle Dalton

FOR PATIENTS WITH DIABETIC macular edema (DME), intravitreal anti-vascular endothelial growth factor (VEGF) agents have become the first-line treatment. There are currently only two VEGF inhibitors approved for use in the United States for the treatment of DME: aflibercept (Eylea, Regeneron) and ranibizumab (Lucentis, Genentech). Bevacizumab (Avastin, Genentech) is often used off-label, and pegaptanib (Macugen, Bausch + Lomb) has declined in use since the introduction of both aflibercept and ranibizumab.

Numerous clinical trials have shown both visual acuity (VA) and anatomic outcomes can be improved with the use of the anti-VEGFs, yet reports of persistent DME remain despite continuous anti-VEGF therapy. Extension studies of RESTORE, RISE and RIDE all show a decline in VA when patients were transitioned to a more flexible treatment after being on a fixed dosing regimen.1, 2

The SWAP-TWO study3 was a prospective, interventional, single-arm study (Cole Eye Institute) that enrolled 20 eyes of 20 patients between December 2015 and August 2017 to evaluate the effects of switching patients with DME to aflibercept after being previously treated with other anti-VEGF agents; the study also placed these patients on a fixed dosing regimen. This initial six-month interim analysis suggests switching agents can substantially improve anatomic outcomes while maintaining vision gains.

In SWAP-TWO3 eligible participants were aged ≥ 18 years with foveal-involving retinal edema secondary to diabetic retinopathy (DR) based on investigator review of clinical exam and spectral-domain optical coherence tomography (SD-OCT) with central subfield thickness of 325 μm, best-corrected visual acuity (BCVA) of 20/25 to 20/400 in the study eye, and history of previous treatment with bevacizumab or ranibizumab with at least four previous injections in the last six months. Patients were excluded if they had a history of aflibercept use, or if they had used systemic anti-VEGF therapy in the three months prior to enrollment. The average age at screening was 63.7 years, 13 enrolled subjects were female (65%), and the average number of prior injections was 4.25 during the six months prior to study enrollment. Nine of the eyes were considered to have moderate DR severity, and the mean central subfield thickness was 419.7 μm in the study eye. The majority of patients had been treated with bevacizumab (95%).

Patients were administered 2 mg (0.05 mL) of intravitreal aflibercept administered monthly until there was no evidence of fluid as determined by OCT. (For this study, “no evidence of fluid” was considered to include lack of subretinal fluid, a central subfield thickness of < 320 μm, or a foveal cystoid macular edema with focal depression present or with fovea flat.)

Patients were administered fixed aflibercept once every two months; “failure” was defined as a loss of 15 or more ETDRS letters from the best previous measurements and an increase of 75 μm compared to the previous visit measurement. The investigators allowed an additional treatment with aflibercept for those patients.

The primary outcome of the study was defined as the mean absolute change from baseline central foveal thickness at month 12 with pre-planned interim analysis as measured by SD-OCT (defined as the average thickness within the central 1 mm subfield) at month 6. Secondary outcomes included the efficacy of treatment outcomes by improvements in ETDRS BCVA from baseline, perfusion changes in OCTA before and after therapy, as well as safety and tolerability of aflibercept therapy by monitoring adverse events.

TAKE-HOME

Study found improvements could be achieved when switching patients to aflibercept from other anti-VEGFs. The study confirms findings from other retrospective studies.

For patients with diabetic macular edema, intravitreal anti-VEGF agents have become the first line treatment. (Image courtesy of SWAP-TWO study)
annual visual field tests for those without fast disease progression.

"It is well worthwhile and I explain to the patient why we are doing this, that some people get rapidly worse," he said. "I also explain that at the end of doing this series of tests, we will know that patient is one of the people who will not get worse very fast at all and that patient can be re-assured."

However, better biomarkers are needed to reveal if patients with glaucoma are getting worse and at risk of losing their vision, Dr. Quigley pointed out.

Additionally, glaucomatous eyes have been observed to not display the same degree of change in the lamina in response to IOP reductions as non-glaucomatous eyes. This observation and understanding the biomechanics of the sclera has led to new insights into the pathogenesis of glaucoma and has revealed new therapeutic targets and novel treatments like rho-associated protein kinase (ROCK) inhibitors. (Transl Vis Sci Technol. 2018 Nov 14;7(6).)

**SUSTAINED-RELEASE DELIVERY**

Success in animal models is pointing to the sustained release of dorzolamide as a way to lower IOP and protect against the loss of retinal ganglion cells.

In both rat and rabbit glaucoma models, Dr. Quigley and colleagues have achieved success with the injection of the therapy as microparticles, to halt the progression of glaucoma. (Mol Pharm. 2016 Sep 6;13(9):2987-95. Transl Vis Sci Technol. 2018 Mar 28;7(2):13.)

“We have produced three-month long pressure-lowering (of IOP) with delivery of one treatment,” Dr. Quigley noted. “The hope is that it will get to six months (between treatments).

Going forward, researchers hope to take their work to the next step. The ultimate goal is ensuring that patients have positive results and improved quality of life.

Translating this animal research to patients is clearly possible, so that the future scenario of glaucoma treatment would mean patients make a visit to the ophthalmologists a couple of times in the span of a year.

“You would inject the patient every six months, and the patient would get in the car and drive home,” he concluded. “That should be quite feasible.”

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Ophthalmology Times
Color-LED topography measures corneas regularly

Guidelines for anterior topography, aberrometry, total corneal astigmatism established

By Laird Harrison; Reviewed by David P. Piñero, PhD

Color light-emitting diode (LED) technology can consistently measure anterior topography, aberrometry, and total corneal astigmatism, according to David P. Piñero, PhD.

But these measurements cannot be used interchangeably with those obtained through Scheimpflug imaging by the Oculus Pentacam, said Dr. Piñero of the University of Alicante, in Alicante, Spain.

He presented the findings at the European Society of Cataract and Refractive Surgeons (ESCRS) annual meeting.

The Cassini Total Corneal Astigmatism is a multi-spot (up to 700), multi-color (red, yellow and green) LED tear film-reflection topography imaging system designed to avoid source mismatch and decrease artifacts caused by shadows.

The system uses ray tracing to process every three spots identified by the software and to define the relevant local elevation. Employing the reflection of seven infrared LEDs for Second Pukinje imaging, it measures the center of the posterior corneal surface.

Dr. Piñero and colleagues set out to evaluate the intrasession repeatability of anterior corneal topographic and aberrometric measurements obtained by the Cassini and to compare it with those obtained by the Pentacam in healthy eyes.

**COMPARISONS**

They made this comparison in 35 healthy eyes of 35 patients, with an age range of 16-66 years at the University of Alicante. They obtained three consecutive measurements in each patient to assess the intrasession repeatability. Then they obtained one measurement in each patient with the Pentacam system.

The research team discovered that the within-subject standard deviation for keratometric readings was 0.02 mm with intraclass correlation coefficient readings of at least 0.992.

In addition, the team also found that the intrasession repeatability for anterior astigmatic measurements was 0.16 D, and for total astigmatic measurements it was 0.05 D. The intraclass coefficient readings were 0.930-0.978.

They found a standard deviation of 0.06 mm for asphericity and 0.03 mm for corneal diameter, “which can also be considered as a good level of intrasession repeatability,” said Dr. Piñero.

When analyzing the repeatability of aberrometry, however, the researchers found “something curious,” Dr. Piñero explained. “We obtained very good correlation coefficients and intraclass correlation coefficients.”

Dr. Piñero noted that within subject standard deviations, for all this Zernike terms for the second order to the fourth order.

“But when we analyzed one component of the secondary astigmatism and one component of the quadrafoil, we obtained a limited intrasession repeatability,” he said.

**TAKE-HOME**

Researchers evaluated the intrasession repeatability of anterior corneal topographic and aberrometric measurements obtained by the Cassini and compared it with those obtained by the Pentacam in healthy eyes.

**CONCLUSIONS**

Armed with this information, the research team is poised to continue its work to find additional commonalities.

“More studies are needed to corroborate this consistency of Cassini measurements in pathological or highly aberrated corneas,” Dr. Piñero concluded.

“There are no studies evaluating the repeatability in keratoconus, for example, or the interchangeability with other currently available topography systems also based in Scheimpflug images.”

Dr. Piñero has no financial interests in the subject matter.
“Tired, itching eyes, blurred vision, headaches, sore neck and shoulders... we’ve been seeing lots of Netflix-Binge Disorder lately.”

Artwork by Jon Carter

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