

News in Review

COMMENTARY AND PERSPECTIVE

RETINA

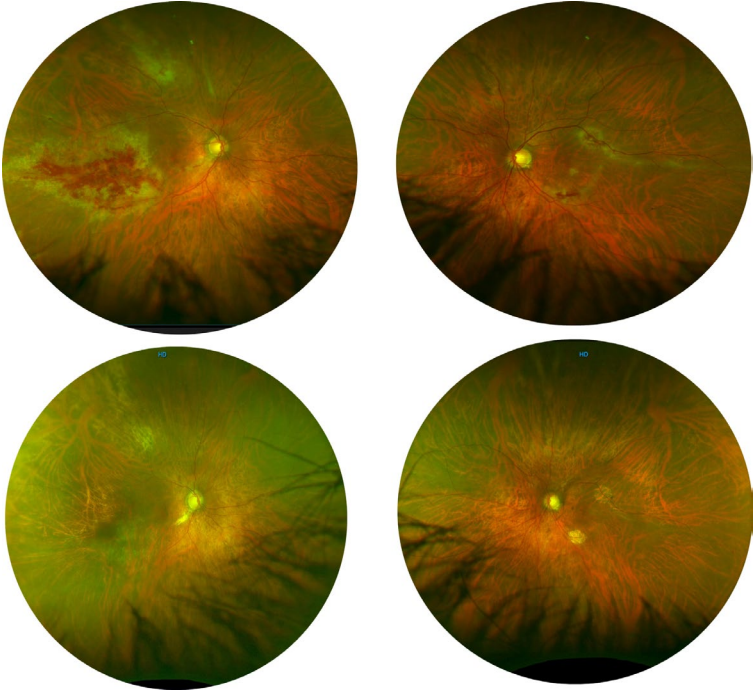
Adoptive Immunotherapy Targets CMV Retinitis

INFUSIONS OF CYTOTOXIC T-CELLS are offering hope to patients who are refractory to or intolerant of current therapies for cytomegalovirus (CMV) retinitis. The novel therapy involves CMV-specific cytotoxic T lymphocytes (CTLs)—and despite the immune privilege status of the eye, infusion of these cells led to resolution of CMV retinitis in 90% of treated eyes in a small study.¹

Adoptive cell transfer. The treatment was originally developed for cancer patients, said Szilárd Kiss, MD, at Weill Cornell Medical College in New York City. A team of researchers at Memorial Sloan-Kettering Cancer Center developed a library of CMV-specific CTLs from a pool of T-cell donors, and each CMV CTL line was genotyped for the human leukocyte antigen system.

“The broad concept is that you and I have T cells that recognize CMV, and we can take those T cells and bank them,” Dr. Kiss said. When a patient comes in with resistant CMV, “we can take the T cells that match [the patient]—and it doesn’t even have to be an exact match.” The treatment essentially re-establishes the patient’s immune cell activity against CMV, Dr. Kiss said. “Your immune system is trained to fight off CMV even after the infused donor cells are gone.”

Study specifics. For this study, Dr. Kiss and his colleagues evaluated



BILATERAL DISEASE. This patient had HIV, active lymphoma, and CMV retinitis. Despite receiving twice-weekly intravitreal injections and systemic treatment with antivirals for the retinitis, the disease was progressively worsening and threatening his vision. (Top) Active CMV retinitis at presentation. Polymerase chain reaction (PCR) results showed 1.5×10^7 CMV viral particles in the right eye and the UL97 mutation. Treatment involved four rounds of CTL infusions. Oral medication for CMV retinitis was discontinued because of severe side effects; intravitreal injections also were discontinued. (Bottom) Nearly three years following the CTL infusions, no signs of disease are evident in either eye. A follow-up PCR for CMV also was negative. The patient continued to be severely immunocompromised due to his ongoing treatment for recurrent lymphoma.

the ocular outcomes of a subset of 27 patients who were treated for CMV retinitis at Weill Cornell Medical College. The subset comprised seven patients (10 eyes) who received infusions of CMV-specific CTLs. All seven were men; their average age was 53 years (range, 26-68 years). All had undergone treatment with systemic and intravitreal antiviral medications, and their average best-corrected visual acuity (BCVA) at baseline was 20/91 (range, 20/20 to counting fingers).

During an average follow-up of 30 months (range, 6-76 months), the

CMV retinitis resolved completely in nine of the 10 eyes, even in light of continued immunosuppression of the patients. Mean BCVA at final follow-up was 20/78 (range, 20/20 to no light perception). No immune recovery uveitis was noted.

Potential recipients. During the HIV epidemic, CMV retinitis was a risk for many AIDS patients, Dr. Kiss noted. “Now, the face of CMV retinitis is transplant patients, who are facing indefinite immune suppression, and cancer patients, specifically those who’ve undergone bone marrow transplantation.”

Standard care for CMV retinitis primarily involves antiviral therapy with agents such as ganciclovir and foscarnet. However, “there are refractory cases that are resistant to standard therapy,” said Dr. Kiss. In particular, certain mutations in the virus render patients CMV resistant. Moreover, as he noted, “some patients are intolerant to standard care, which may require bone marrow-suppressing systemic treatment.”

For these patients, who have no other options, this therapy is a game-changer, Dr. Kiss said. He offered the example of a patient with the relevant antiviral resistance mutations. “After four infusions, he’s cured—although the patient’s immune system is still compromised, because he had a bone marrow transplant.”

Next steps. “We’ve received inquiries from around the world for patients

who have CMV retinitis—and even CMV esophagitis that is ravaging their gut,” Dr. Kiss said. But availability is an issue, as patients currently need to come to New York for treatment. “Memorial Sloan-Kettering is trying to figure out how to make this therapy available to more patients. The hope is that a commercial partner will step up,” he said.

And as Dr. Kiss and his colleagues noted, additional studies are needed to evaluate the treatment’s safety and efficacy in a larger group of patients and to clarify whether it is best used as monotherapy or as an adjunctive treatment.

—Jean Shaw

1 Gupta MP et al. *Ophthalmol Retina*. 2021;5(9): in press.

Relevant financial disclosures—Dr. Kiss: Intellectual property related to CTL treatment assigned to Cornell University.

PEDIATRICS

Botox Versus Surgery for Strabismus

EXTRAOCULAR MUSCLE INJECTION of botulinum toxin type A (BTXA) achieves a high rate of successful motor alignment comparable to eye muscle surgery in children and adults with nonparalytic, nonrestrictive horizontal strabismus. The finding is in an *Ophthalmic Technology Assessment (OTA)* from the Academy.¹

“BTXA is a good alternative to eye muscle surgery for certain clinical situations,” said Gil Binenbaum, MD, MSCE, at Children’s Hospital of Philadelphia. “Both modalities can successfully treat strabismus, and each approach has advantages and disadvantages that might make it preferable in a given situation.” Moreover, the evidence

CATARACT

Update on Sequential Bilateral Cataract Surgery

AN ANALYSIS OF REFRACTIVE OUTCOMES AFTER SE-quential bilateral cataract surgery revealed that surgery performed on both eyes on the same day was associated with worse visual acuity than was delayed sequential surgery.¹ While differences between cohorts were small, they may take on clinical relevance in the presence of additional variables such as age, ethnicity, and selected ocular comorbidities.

The findings are based on electronic medical records of nearly two million patients who underwent sequential bilateral cataract surgery, as reported in the Academy’s IRIS Registry.

Better to delay? The researchers analyzed visual outcomes following immediate and delayed sequential bilateral surgery. The latter category was further divided into two groups of patients: 1) those who had surgery in the second eye one to 14 days after the first surgery and 2) those who had the second surgery 15 to 90 days after the first.

After the researchers controlled for variables, immediate sequential surgery was associated with lower uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) by 2.79 and 1.64 letters, respectively, when compared with delayed surgery.

Unexpectedly, patients who had the second surgery

within 14 days of the first had better outcomes than did those who waited up to 90 days (0.41 and 0.89 letters, respectively; $p < .001$ for both).

Confounding variables. Older age, Black and Asian ethnicity, Medicaid coverage, previous history of glaucoma, and the presence of diabetic retinopathy (DR) or age-related macular degeneration were independently associated with worse visual outcomes.

“The associations between non-White race and Medicaid coverage were somewhat unexpected,” said Cecilia S. Lee, MD, MS, at the University of Washington in Seattle. Specifically, Medicaid beneficiaries had worse outcomes than those on Medicare, and Asian and Black patients had worse VA by approximately 1 letter and 0.5 letter, respectively, than did the White patients.

Controlling for surgical volume did not affect the current results, although other studies have found that visual outcomes are associated with the surgical volumes of the cataract surgeons.

Limited clinical impact? Although statistically significant, the findings were deemed not clinically relevant, as 1 or 2 letters do not mean much clinically. “Ophthalmologists need to keep this in mind when interpreting our study results and considering them for clinical decision-making,” Dr. Lee said.

But having said that, she also noted that a patient with several risk factors may be more likely to have worse visual outcomes that could be clinically significant after immediate sequential surgery.

As an example, she said, an older Asian patient with

indicates that BTXA is effective as an alternative treatment for reoperations following prior eye muscle surgery, Dr. Binenbaum said.

Searching for evidence. For this *OTA*, the Pediatric Ophthalmology/Strabismus Panel conducted a systematic review of evidence that yielded 515 citations. Of these, 14 met inclusion criteria and were graded as either level II (n = 5) or level III (n = 9) evidence. No studies were graded as level I.

In children, the findings applied to both initial treatment and repeat treatment of strabismus after prior horizontal eye muscle surgery. Most patients in the comparative studies had esotropia.

Findings. Across four of the five level II comparative studies, success after Botox injections was relatively consistent at 60%, while success after surgery ranged from 66% to 77%. The fifth level II study reported significantly higher



CANDIDATE? Most patients in the reviewed comparative studies had esotropia. Both esotropic and exotropic patients were represented in the case series.

success with BTXA injection compared to surgery (94% vs. 72%).

In the level III case series, higher motor success rates of 87% to 89% were reported when children were treated in two muscles at a time. In adults treated with single injections, successful alignment rates were lower, suggesting that bilateral injections of BTXA may more effectively help to achieve the desired outcome.

Dosing. Although the doses used in the reviewed studies varied, in general, they were 2.5 to 5 units of BTXA injected into each muscle, with higher doses used for repeat injections. The number of sets of injections typically ranged from one to three—and for each set, one or two muscles were injected.

Side effects. Injection of BTXA appears to be relatively safe, with few or no lasting adverse effects, the *OTA* concluded. The most common side effects were transient ptosis and transient vertical strabismus; no blinding complications were reported.

An expected strabismus in the direc-

tion opposite of that being treated occurred in essentially all patients, but it resolved in most cases, as the BTXA effect dissipates over time.

Bottom line. “The literature clearly suggests that BTXA and eye muscle surgery have comparable motor success rates for basic strabismus,” Dr. Binenbaum said.

But further research, particularly from one or more well-designed randomized trials, is needed. As the *OTA* pointed out, “A study comparing time to desired alignment and binocular visual outcomes regardless of the number of eye muscle surgeries or sets of BTXA injections may help surgeons to understand better the relative benefits of either approach.”

In particular, Dr. Binenbaum noted, “there is limited evidence about sensory outcomes.” Moreover, when compared to eye muscle surgery, which achieves alignment quickly, it’s possible that the longer time frame needed for achieving good alignment with BTXA could negatively affect sensory outcomes, he said.

For now, Dr. Binenbaum is more open to considering BTXA in certain pediatric cases. “It is easy and quick to perform, it can work as well as eye muscle surgery, and for some children it may be preferable.” —*Miriam Karmel*

1 Binenbaum G et al. *Ophthalmology*. Published online June 24, 2021.

Relevant financial disclosures—Dr. Binenbaum: Luminopia: O; X-Biomedical: O.

DR and Medicaid coverage could be expected to see approximately 1 Snellen line less than a younger White patient who has no DR and is covered by Medicare.

Looking ahead. Further research—including investigations of other potential confounders—may reveal ways to improve refractive outcomes in high-risk groups, Dr. Lee said. For now, given the minimal difference in VA associated with timing of the second surgery, both same-day and delayed approaches are acceptable for most patients, she said. “However, if a patient has multiple risk factors for worse visual outcomes, a delayed approach may be considered.” (For more, see Journal Highlights, page 22.)

—*Miriam Karmel*

1 Owen JP et al. *JAMA Ophthalmol*. Published online July 1, 2021.

Relevant financial disclosures—Dr. Lee: Klorfine Family Endowed Chair: S; National Institute on Aging: S; Research to Prevent Blindness: S.

MORE AT AAO 2021

SAME-DAY BILATERAL CATARACT SURGERY (SYM07).

When: Saturday, Nov. 13, 11:30 a.m.-12:45 p.m. **Where:** New Orleans Theater AB.

DIFFICULT STRABISMUS PROBLEMS: DIAGNOSIS AND MAN-

AGEMENT 2021 (237). **When:** Monday, Nov. 15, 11:30 a.m.-12:45 p.m.

Where: Room 283.

HOW TO RECOGNIZE AND TREAT INFECTIOUS UVEITIS (452).

When: Sunday, Nov. 14, 2:00-3:15 p.m. **Where:** Room 288.

AAO
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See the financial disclosure key, page 8. For full disclosures, including category descriptions, view this News in Review at aao.org/eyenet.