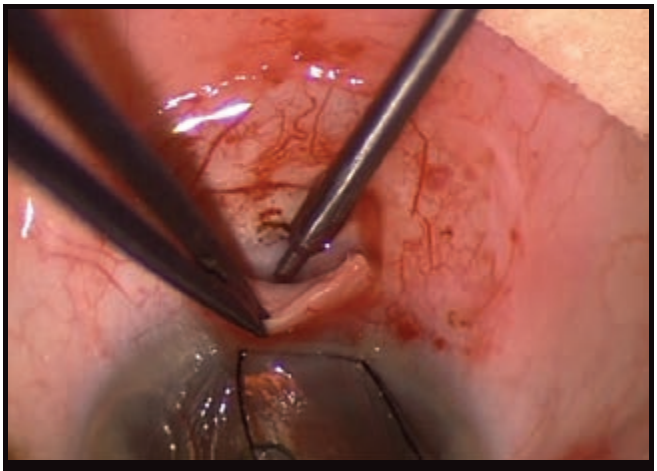
BAK Dose Response in Surgical Outcomes

The antiglaucoma drops you prescribe today may lead to surgical failure down the road. That's the conclusion of a study evaluating the relationship between exposure to benzalkonium chloride (BAK), the most frequently used antiglaucoma drop preservative, and subsequent risk of filtration surgery failure.[1] It found that the risk of early failure increased by a factor of 1.21 for each additional drop containing BAK that is administered each day.

"Presurgical treatment can have a very relevant influence on the outcomes of surgery," said Catherine M. Birt, MA, MD, FRCSC, one of the study authors and associate professor of ophthalmology and vision sciences, University of Toronto.

Surprisingly, the number of medication classes used had no impact on time to failure. Whether the person was on one, two, three, or four classes of glaucoma medication did not affect the outcome, said Dr. Birt. "What mattered was how many of the drops contained BAK."

The study. The retrospective chart review looked at 128 glaucoma patients who had undergone a trabeculectomy and reviewed the number and type of ophthalmic drops used preoperatively. It measured outcome in terms of complete surgical success, qualified success, or surgical failure. Complete surgical success was defined as reduced IOP and no need for additional surgery, no bleb revisions later than six weeks after surgery, and no need for postoperative ocular antihypertensives. Qualified successes needed some additional treatment but no further incisional surgery. Complete failures required additional surgery.



SURGICAL SUCCESS. The eyedrops that a patient takes before trabeculectomy may affect the success of the surgery, according to one study.

Potentially confounding variables, including age, sex, race, previous phacoemulsification, and duration of intraoperative MMC exposure, did not affect the results; nor did disease severity. However, a diagnosis of uveitic or neovascular glaucoma did result in a greater chance of surgical failure.

In the clinic. The authors noted that the medications used by patients in the study contained varying concentrations of BAK, ranging from 0.005 to 0.02 percent. When the researchers multiplied the drops taken by the concentration of BAK within each drop to get a total dose of BAK, they found a statistically significant association on the outcome.

FOCAL POINTS 2000;18(6):6.

"In the clinical situation, it is easier just to add up the [BAK-containing] drop count," Dr. Birt said.

To minimize BAK exposure, Dr. Birt may prescribe BAK-free alternatives, including Cosopt Preservative Free, Travatan Z (which contains a preservative called sofZia), and Alphagan P (which contains Purite). Regarding generic options, she said, "It is hard to be sure what each generic is preserved with—there are so many out there. If I want to be sure that BAK is not given, I write 'no substitute' on the prescription."

Should a patient switch to a BAK-free drop prior to surgery? "I am not sure how long it takes for the effect to wear off, but if there is an interval of a few weeks, it might be worthwhile," said Dr. Birt.

Regarding this study, she said, "The most important finding is the strong clinical and statistically significant relationship between the amount of preoperative BAK exposure and the time to surgical failure."

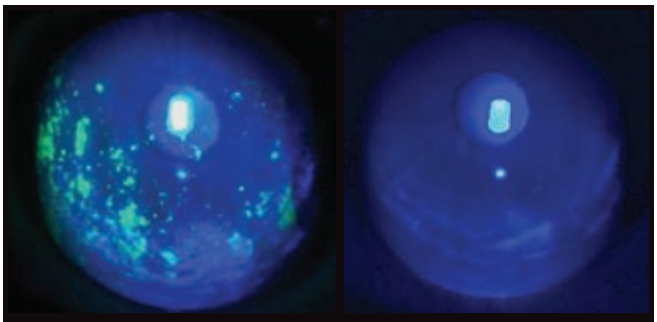
—Miriam Karmel

1 Boimer C, Birt CM. *J Glaucoma.* 2013 March 20. [Epub ahead of print].

***Dr. Birt** is on the speakers bureau for Alcon, Merck, and Pfizer.*

Cornea Report

Biologic Treatment for Dry Eyes?



BILATERAL CORNEAL FLUORESCEIN STAINING CLEARANCE. An eye treated with anakinra over 12 weeks.

In the quest to find a highly specific, protein-based biologic to treat dry eye disease (DED), researchers in Boston may have hit upon a promising agent. Their study of 75 patients with refractory DED demonstrated the efficacy of topical interleukin-1 (IL-1) blockade.[1]

Study findings. Producing a rapid response at both 2.5 and 5 percent concentrations, a recombinant version of human interleukin-1 receptor antagonist (IL-1Ra) called anakinra (Kineret) was six times more effective at reducing the symptoms of dry eye than an eye lubricant, as measured by the Ocular Surface Disease Index (OSDI). Anakinra is currently FDA approved as a second-line treatment for rheumatoid arthritis and used off label for other systemic conditions involving IL-1–mediated inflammation.

In the prospective double-masked, randomized, controlled trial, patients receiving the lower dose were also four times more likely to achieve bilateral corneal fluorescein staining (CSF) clearance at 12 weeks than were patients treated with eye lubricant. "This is the first time, to my knowledge, that any dry eye drug has reached this milestone," said senior author Reza Dana, MD, MSc, MPH, coinventor of the treatment, director of cornea at the Massachusetts Eye and Ear Infirmary, and professor of ophthalmology at Harvard Medical School. "Both corneas of nearly one-third of the subjects treated with one of the IL-1Ra doses went from being diseased to totally clear."

Although the 5 percent concentration produced an early reduction in CFS clearance, a regression back toward baseline later occurred, said Dr. Dana. "This was not a big surprise because we do not see a classic dose-response relationship with many anti-inflammatory therapies, such as with topical cyclosporine, as shown in clinical trials." Regression toward baseline in both signs and symptoms also occurred in patients who suspended treatment after week 12, as per protocol, confirming the therapeutic effect of the drug.

Among other efficacy endpoints, Schirmer test scores did not change, indicating that targeting the IL-1 molecule can promote ocular surface epithelial health without necessarily promoting increased tear secretion, said Dr. Dana.

Anakinra vs. other agents. Applied as a single drop three times daily for 12 weeks in both eyes, anakinra was also very well tolerated, causing no serious ocular or systemic adverse events. This may provide an advantage over nonspecific immunomodulatory or immunosuppressive agents such as corticosteroids and tetracycline derivatives.

The rapidity of symptom relief with this biologic approach also differentiates it from topical cyclosporine, which can take several months to achieve results. Dr. Dana suggested that one possible reason for this is that IL-1 has been linked with pain perception. "IL-1 blockade is likely efficacious," he said, "not only because it suppresses dry eye disease–related inflammation on the ocular surface, but also because it suppresses the patient's perception of discomfort."

1 Amparo F et al. *JAMA Ophthalmol.* 2013 April 18. [Epub ahead of print].

***Dr. Dana** is listed as a coinventor on patent applications licensed by the Schepens Eye Research Institute and Massachusetts Eye and Ear Infirmary to Eleven Biotherapeutics, in which he holds an equity position.*

REZA DANA, MD, MSC, MPH

New Glaucoma Tool

Predicting Adherence

You prescribe a glaucoma drop, but will your patient take it? It's hard to tell. Now researchers have developed a scoring system to help physicians predict which patients may be less likely to adhere to their regimen.[1]

The simple scoring tool identifies six characteristics to estimate the probability that a patient will be nonadherent: younger age, black race, worse general health, shorter duration of glaucoma medication therapy, lower self-reported adherence, and admitting to not following doctors' orders.

Patients who don't know the names of all their medications and patients with no family history of glaucoma are also more likely to miss their eyedrops. However, those strong predictors emerged too late in the study to be included, said Michael V. Boland, MD, PhD, assistant professor of ophthalmology and director of information technology, Wilmer Eye Institute.

Adherence was defined as taking drops within four hours of the average dosing time. An adherence rate of 75 percent or less was classified as nonadherent. Interestingly, very few patients reported cost, side effects, or other medical conditions as barriers to adherence.

Researchers developed the model using the Travatan Dosing Aid study (n = 196). Then they validated the model in the Automated Dosing Reminder Study (n = 407). In each study, patients had taken once-daily prostaglandin eyedrops from electronically monitored bottles.

This is the first study providing a validated scoring system for predicting a patient's eyedrop-taking behavior, Dr. Boland said. "All of the variables are things that could be known about each patient without much additional work on the part of the provider."

—Miriam Karmel

1 Chang DS et al. *Ophthalmology.* 2013 March 29. [Epub ahead of print].

***Dr. Boland** reports no related financial interests. The study is funded by the Microsoft Be Well Fund, which had no role in the design or conduct of the research.*

Pediatrics Update

Retinoblastoma Tumor: New Form Discovered

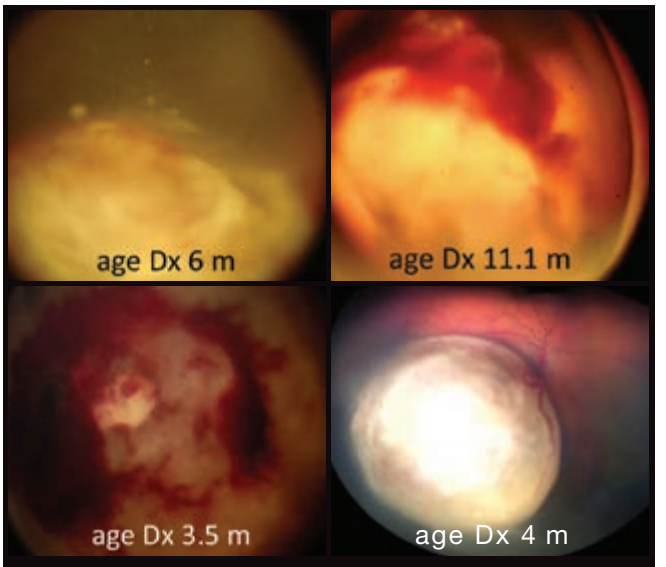
A new type of rapidly developing retinoblastoma affecting young babies has been identified by Brenda Gallie, MD, professor in the faculty of medicine at the University of Toronto, in collaboration with an international team.[1]

Although it was long thought that all cases of retinoblastoma were caused by loss of the *RB1* gene, Dr. Gallie said molecular diagnostics have clarified that there is more to the story. In some very young infants, a powerful oncogene can drive an aggressive form of this cancer that starts long before birth in babies whose families have no history of the disease.

"These tumors are distinctly different, and that is a very exciting discovery," Dr. Gallie said.

Researchers analyzed more than 1,000 primary unilateral nonfamilial retinoblastoma tumors to validate the finding. Early age of onset predicts that about one-fifth of babies diagnosed at younger than 6 months of age have this form of cancer, rather than inherited retinoblastoma.

The earliest diagnosis often comes when parents observe a white pupil in the eye of the child. "Doctors commonly think to save the first eye in young unilateral patients, but the data show that this is dangerous with these fast-growing tumors," she said. "Clinicians need to know the situation is urgent. What is needed is to get that eye out. If we are aggressive, we protect the child. Following surgery, they [the children] are normal, and not at risk for other cancers."



PRESENTATION. Four examples of clinical appearance of the nonhereditary retinoblastoma tumor.

Since this form of cancer is not inherited, siblings and offspring are not at risk.

The discovery has huge implications for further understanding of human cancers and potential therapies, Dr. Gallie said.

—Laura Kaufman

1 Rushlow DE et al. *Lancet Oncol.* 2013;14(4):327-334.

***Dr. Gallie** is the unpaid medical director of Impact Genetics.*

LANCET ONCOL. 2013;14(4):327-334.