OCULOPLASTICS

New Drug Targets Challenge of Thyroid Eye Disease

FOR THE FIRST TIME, A MEDICATION has been approved that can stop and modify the debilitating and sight-threatening pathology of thyroid eye disease. Teprotumumab (Tepezza) gained expedited approval from the FDA in January.

The drug is a fully human monoclonal antibody inhibitor of the insulin-like growth factor I receptor (IGF-IR), which orbital fibroblasts and B and T cells overexpress in Graves disease and thyroid eye disease (TED).[1]

TED "is really burdensome for patients. It impairs their vision, in addition to causing their facial disfigurement and double vision. Teprotumumab is the first medication that reverses all of those things, and with mild to moderate side effects," said Raymond S. Douglas, MD, PhD, one of the principal investigators in OPTIC, the study that led to the FDA's approval. "My patients are just thrilled. This has been a real game-changer."

OPTIC results. Earlier this year, researchers published results of OPTIC, a phase 3 trial.[2] In this study, 41 patients with TED received a total of eight intravenous infusions of teprotumumab, spaced three weeks apart. They showed significantly greater improvement in their disease at 24 weeks than did the 42 participants who received placebo.

The trial achieved its primary outcome—a reduction in proptosis of 2 mm or more—in 83% of the treated patients at 24 weeks. This compared to 10% in the placebo group ($p < 0.001$).

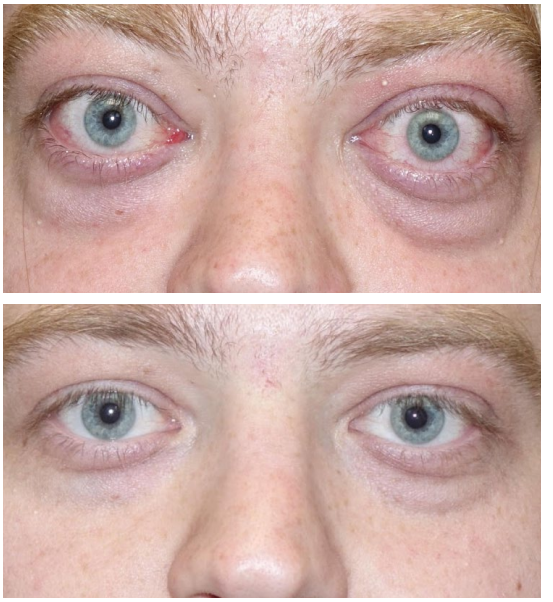
Early disease improvement. More than half of the treated patients (56%) reached this study marker in as few as six weeks, and they continued to improve through 24 weeks, said Dr. Douglas, at Cedars-Sinai Medical Center in Los Angeles.

Additional findings. The study also found significantly greater improvements in the treated patients' secondary outcomes ($p \leq 0.001$ for all), the researchers reported. These clinical measures included overall response (78% of treated patients vs. 7% of the placebo group); Clinical Activity Score of 0 or 1 (59% vs. 21%); the mean change in proptosis (−3.32 mm vs. −0.53 mm); and diplopia response (68% vs. 29%).

In addition, improvement was noted in a 16-item quality of life (QoL) questionnaire specific to Graves disease (mean change of 17.28 points in treated patients vs. 1.80 points in the placebo group). This self-administered questionnaire includes questions on visual and psychosocial functioning; a mean change of at least 6 points is considered clinically significant.

Side effects. Adverse events associated with the drug were mild to moderate in most cases and included muscle spasms (32%), alopecia (20%), nausea (15%), fatigue (12%), and diarrhea and headache (both 10%), the researchers reported. There were two serious adverse events: an infusion reaction that resolved with corticosteroid treatment, and pneumothorax that was considered unrelated to the drug.

Mechanism of action. Previous research has shown that teprotumumab blocks the pathologic immune responses of active TED by reducing signaling by both IGF-IR and thyrotropin receptors.[1] Unchecked, the activated receptors lead to the formation of physical and functional molecular complexes that trigger hyaluronan accumulation and expression of cytokines, which in turn cause inflammation, edema, and expansion of



EFFECT OF TREATMENT. *A patient with thyroid eye disease before and after treatment with teprotumumab. The drug was administered intravenously once every three weeks during the 24-week trial; evaluation of effectiveness is continuing beyond that point.*

Raymond S. Douglas, MD, PhD

extraocular muscle and adipose tissue, Dr. Douglas said.

It is not clear how long the drug's ability to inhibit the receptors will persist beyond 24 weeks, Dr. Douglas said. The drug manufacturer is conducting a postmarketing study intended to help clarify this issue, he said.

A new paradigm? Looking ahead, the approval of teprotumumab represents "a pivotal moment" in the treatment of TED, Dr. Douglas said. "I consider this a generational medication. I think our fellows who are training now will be hard-pressed to remember the times before teprotumumab came on the market for TED, much like the times before biologics came on the market for rheumatoid arthritis" and revolutionized treatment for that disease. *—Linda Roach*

1 Smith TJ, Janssen JAMJL. *Endocr Rev.* 2019; 40(1):236-267.

2 Douglas RS et al. *N Engl J Med.* 2020;382(4): 341-352.

Relevant financial disclosures—Dr. Douglas: Horizon Therapeutics: C.

PUBLIC HEALTH

Rapid Survey of Blindness: RAAB Method Accurate

RESEARCHERS LED BY A TEAM BASED in Hong Kong set out to assess the diagnostic accuracy of the survey method known as RAAB (for rapid assessment of avoidable blindness). They found that RAAB has high diagnostic accuracy for the detection of the prevalence of blindness, visual impairment (VI), and VI due to cataract.[1] "RAAB is a valuable alternative in areas where cost and logistical factors prohibit the use of conventional epidemiologic surveys," said coauthor Dennis S.C. Lam, MD, FRCOphth, at the Chinese University of Hong Kong.

A note on RAAB. This method is endorsed by the World Health Organization for population-based surveys of blindness and VI in people aged 50 years and older in a specific geographic area. Each RAAB survey involves an eye examination, with the use of a penlight, and a fundus exam via direct ophthalmoscopy. The exams are held in the participant's home. "The major advantages of this method are its simplicity, rapid conduct, lower cost, and use of standardized assessments," said Dr. Lam.

In the field. This study involved 2,145 people aged 50 years and older in 45 villages located in the Chaonan Region of southern China. All participants were examined according to the RAAB protocol; they were then offered a more extensive examination in a mobile eye clinic that was set up in a village center on the same day.

Exams in the mobile clinic included standardized visual acuity (VA) tests using logMAR charts, refraction, slit-lamp biomicroscopy, and a dilated fundus exam with a binocular indirect ophthalmoscope. Blindness and economic blindness were defined as having VA in the better-seeing eye of <20/400 and <20/200, respectively. VI was defined as having VA of <20/60 in the better eye. The primary cause of

REFRACTIVE

SMILE Approval Expanded

THE RESULTS OF A PIVOTAL CLINICAL TRIAL ARE OUT, paving the way for expanded FDA approval of small incision lenticule extraction (SMILE) for the correction of myopia and astigmatism.[1]

Since 2011, SMILE has evolved from a treatment for myopia to one for myopia with astigmatism up to –0.50 D—and now to one for correction of myopia with or without astigmatism up to –3.0 D. The flapless treatment, which reshapes the cornea using only a femtosecond laser, proved safe and effective and demonstrated predictable correction over the trial duration of 12 months, and patients achieved refractive stability between three and six months.

In the approved range, the procedure can be recommended to patients as an alternative method of refractive vision correction, said Jon G. Dishler, MD, at Dishler Laser Institute in Greenwood Village, Colorado.

The study. Between March 2015 and July 2016, 357 patients (357 eyes) underwent SMILE in one eye. (Most fellow eyes received excimer laser treatment.) Preoperative sphere ranged between –1.00 and –10.00 D, with manifest spherical equivalent (MSE) up to –11.50 D and refractive cylinder up to –3.0 D.

At 12 months, 95.3% of all eyes were within 0.50 D of emmetropia, 89.0% achieved uncorrected distance visual acuity (UDVA) of 20/20 or better, and 99.0% had UDVA of 20/40 or better. In addition, MSE went from –5.39 at baseline to –0.01 D, and average refractive cylinder went from –1.53 D to 0.18 D.

Complications. Three intraoperative events were associated with difficult lenticule removal and resultant cap tear. All resolved without sequelae at postoperative day one, and patients completed the study with UDVA of 20/20 or better. Eight adverse events occurred postoperatively; none had significant consequences.

Looking ahead. SMILE still does not address hyperopia, mixed astigmatism, or very high levels of astigmatism, Dr. Dishler noted. "But I would estimate that well over 90% of patients in search of refractive vision correction could be served by this procedure." He noted that the U.S. military is currently completing a SMILE study, and he added, "a procedure with rapid recovery without the limitations of a corneal flap is appealing to both patients and doctors." *—Miriam Karmel*

1 Dishler JG et al. *Ophthalmology*. Published online Jan. 14, 2020.

Relevant financial disclosures—Dr. Dishler: Carl Zeiss: C.

blindness and VI was defined according to the cause of VI in the participant's better eye.

Results. Of the 2,145 participants who were screened with RAAB, 327 (15.2%) refused to attend the mobile eye clinic, and two (0.1%) were unable to undergo the more in-depth examination.

Sensitivities ranged from 89.5% to 90.3%, and specificities ranged from 97.7% to 99.3% for detection of different levels of VI—and these results provide "strong support for the diagnostic accuracy of the RAAB methodology for the detection of blindness and VI," the researchers wrote.

With regard to blindness and VI owing to cataract and refractive error, RAAB was highly accurate for cataract but less so for refractive error.

Limitations. The authors noted that it is possible that their results overestimate the impact of cataract and underestimate those of glaucoma and posterior segment diseases on the prevalence of blindness and VI. Nonetheless, they said, the RAAB methodology "remains an important tool for informing research and policy for blindness prevention." *—Arthur Stone*

1 Zhang XJ et al. *Am J Ophthalmol.* Published online Dec. 14, 2019.

Relevant financial disclosures—Dr. Lam: None.

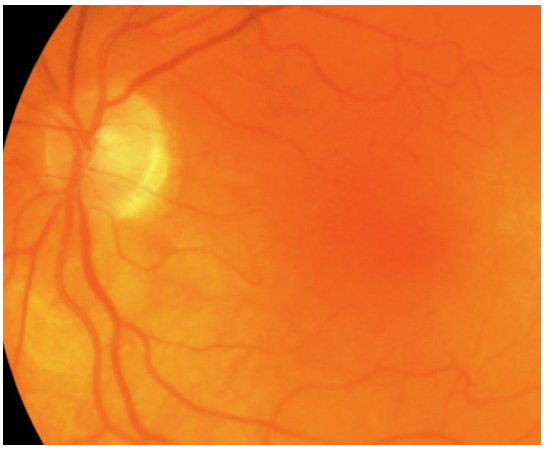
GLAUCOMA

Genetic Test Outlines POAG Risk Categories

A MULTICOUNTRY TEAM HAS DE-veloped a genetic test that stratifies individuals with glaucoma into risk groups.[1] The researchers' polygenic risk score (PRS), or genetic profiling strategy, determines how likely a patient is to develop primary open-angle glaucoma (POAG)—and indicates which patients should be offered early treatment and/or monitoring.

The PRS predicted that individuals in the top decile were at a 15-fold increased risk of advanced glaucoma and 21.5-fold increased risk of advanced high-tension glaucoma, relative to those in the bottom decile. What's more, those in the highest decile reached an absolute risk for glaucoma 10 years earlier than did participants at the bottom.

"Traditionally, genetic testing in glaucoma has focused on rare mutations such as the Gln368Ter variant in the *MYOC* gene. Our work provides the utility of mass screening," said Xikun Han, MSc, at the QIMR Berghofer Medical Research Institute in Brisbane, Australia. "Also, importantly, the prediction can be done before damage begins, and people who are stratified into the high-risk group can take the necessary precautions."



POAG RISK. *The risk calculator was found to be predictive of a number of factors, including earlier age of glaucoma diagnosis, increased likelihood of disease progression in early-stage disease, and greater need for incisional surgery in advanced disease.*

A new approach. Unlike existing risk calculators, which rely on general information such as age and intraocular pressure (IOP), the PRS is based on an individual's profile of all known risk loci for glaucoma. In this study, the researchers identified 107 new gene variants associated with glaucoma that increase the individual's risk of developing POAG.

To create the PRS, the researchers identified vertical cup/disc ratio risk variants from optic nerve photographs of 67,040 participants in the U.K. Biobank, which holds genotyping on 500,000 volunteer participants between the ages of 40 and 69. Thus, this investigation is the largest genome-wide association study of optic nerve morphology to date. In addition to information from the U.K. Biobank, they used other large biobanks to provide risk variants for IOP and POAG.

Age and family history mattered. The PRS, which could be approved for general use in one or two years, was significantly associated with age at POAG diagnosis. Individuals in the top 10% of PRS distribution were, on average, diagnosed seven years earlier than were those in the bottom 10%.

In addition, those in the highest decile had twice as many family members affected by glaucoma as did those at the bottom. Moreover, a higher PRS was associated with a greater need for trabeculectomy.

Room for improvement. The researchers noted that their risk calculator needs to be tested in other populations—and that it could be evaluated prospectively in a longitudinal intervention study. In an effort to improve the PRS' predictive power, the researchers hope to collect DNA from 20,000 people with glaucoma or a family history of glaucoma. "While a more accurate PRS is unlikely to move high-risk individuals to a low-risk category, the current PRS is less accurate for those in the moderately high-risk category," Mr. Han said. "An improved genetic test will help split up this group more effectively, enabling more precise guidance to be given to a larger number of people." *—Miriam Karmel*

1 Craig JE et al. *Nat Genet.* Published online Jan. 20, 2020.

Relevant financial disclosures—Mr. Han: None.

Xikun Han, MSc

See the financial disclosure key, page 10. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.