The observational nature and the lack of standardization in DME management limit definitive conclusions from this study.

Diabetic Retinopathy Clinical Research Network Authors/Writing Committee

Corresponding Author: Talat Almukhtar, MBChB, Jaeb Center for Health Research, 15310 Amberly Dr, Ste 350, Tampa, FL 33647 (dcrctست6@jaeb.org).

Published Online: December 5, 2013. doi:10.1001/jamaophthalmol.2013.6209.

Authors/Writing Committee: The following investigators of the Diabetic Retinopathy Clinical Research Network take authorship responsibility for the study results: Susan B. Bressler, MD; Carl W. Baker, MD; Talat Almukhtar, MBChB; Neil M. Bressler, MD; Paul A. Edwards, MD; Adam R. Glassman, MS; Michael H. Scott, MD.

Authors/Writing Committee Affiliations: Wilmer Eye Institute, The Johns Hopkins University, Baltimore, Maryland (S. B. Bressler, N. M. Bressler); Paducah Retinal Center, Paducah, Kentucky (Baker); Jaeb Center for Health Research, Tampa, Florida (Almukhtar, Glassman); Henry Ford Health System, Detroit, Michigan (Edwards); Medical Associates Clinic, PC, Dubuque, Iowa (Scott).

Author Contributions: Dr Almukhtar had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: S. B. Bressler, Baker, N. M. Bressler, Edwards, Glassman.

Acquisition of data: S. B. Bressler, Baker, Almukhtar, Edwards, Scott.

Analysis and interpretation of data: S. B. Bressler, Baker, Almukhtar, N. M. Bressler, Edwards, Glassman.

Drafting of the manuscript: S. B. Bressler, Baker, Almukhtar, Edwards.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Almukhtar, Glassman.

Obtained funding: N. M. Bressler, Glassman.

Administrative, technical, or material support: Almukhtar, Scott.

Study supervision: S. B. Bressler, Baker, N. M. Bressler, Glassman.

Conflict of Interest Disclosures: A complete list of all DRCR.net investigator financial disclosures can be found at http://www.dcr.net. Grants to investigators at The Johns Hopkins University are negotiated and administered by the institution (such as the School of Medicine) that receives the grants, typically through the Office of Research Administration. Individual investigators who participate in the sponsored project(s) are not directly compensated by the sponsor but may receive salary or other support from the institution to support their effort on the project(s). Dr S. B. Bressler is coinvestigator of grants at The Johns Hopkins University sponsored by Bausch & Lomb, Novartis, and Regeneron and receives grants from EMMES Corp and Notal Vision. Dr N. M. Bressler is principal investigator of grants at The Johns Hopkins University sponsored by the following entities (not including the National Institutes of Health): Bausch & Lomb, Bristol-Myers Squibb, Carl Zeiss Meditec, EMMES Corp, ForSight Labs, LLC, Genentech, Genzyme Corp, Lumenis, Notal Vision, Novartis, and Regeneron. No other disclosures were reported.

Funding/Support: This work was supported through cooperative agreements EY14231 and EY018817 from the National Eye Institute and the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, US Department of Health and Human Services.

Role of the Sponsor: The National Institutes of Health participated in oversight of the conduct of the study and review of the manuscript but not directly in the design or conduct of the study, collection, management, analysis, and interpretation of the data, or preparation of the manuscript.

Group Information: A complete list of the Diabetic Retinopathy Clinical Research Network appears in the Supplement.

Correction: This article was corrected online December 19, 2013, to add group information.


Effect of Azithromycin on Lipid Accumulation in Immortalized Human Meibomian Gland Epithelial Cells

Meibomian gland dysfunction (MGD) is believed to be the leading cause of dry eye disease (DED), which affects tens of millions of Americans. Of particular interest, the most common pharmaceutical treatment for the management of MGD in the United States is the off-label use of topical azithromycin. This macrolide antibiotic is presumed to be effective because of its anti-inflammatory and antibacterial actions, which may suppress the MGD-associated posterior blepharitis and growth of bacteria on the eyelid. However, to our knowledge, no published, peer-reviewed data demonstrate that azithromycin has the ability to act directly on the human meibomian gland to enhance this tissue’s function and to ameliorate the pathophysiology of MGD.

We hypothesize that azithromycin can act directly on human meibomian gland epithelial cells to stimulate their differentiation, enhance the quality and quantity of their lipid production, and promote their holocrine secretion. Our purpose was to begin to test our hypothesis.

Methods: Immortalized human meibomian gland epithelial cells (IHMGECs; passages 20-22) were cultured in the presence or absence of 10% fetal bovine serum as previously reported. Cells were treated with the ethanol vehicle or azithromycin (10 μg/mL; Santa Cruz Biotechnology) for varying periods. Cellular morphological appearance was recorded, cells were counted with a hemocytometer, and lipid accumulation was assessed by staining cells with LipidTOX green neutral lipid stain (Invitrogen Corp) according to reported methods. Staining fluorescent intensities were quantified using ImageJ software (http://rsbweb.nih.gov/ij/index.html). Statistical analyses were performed with t test (2-tailed, unpaired).

Results: Our results show that azithromycin induces a striking, time-dependent accumulation of lipid in IHMGECs (Figure 1A). Within 3 days of azithromycin exposure, the number, size, and staining intensity of intracellular lipid-containing vesicles had markedly increased as compared with those of vehicle-treated control cells. This azithromycin effect on lipids appeared to become maximal at days 3 to 7 of the study (Figure 1B).

Evaluation of cellular morphology indicated that azithromycin may promote terminal maturation of IHMGECs given that vesicle accumulation was often followed by a cell break-up and vesicle release (Figure 1C).
In contrast to these effects, azithromycin reduced the proliferation of IHMGECs. As shown in Figure 2, this result was found irrespective of whether IHMGECs were cultured under proliferation or differentiation conditions.

Discussion | This study supports our hypothesis that azithromycin can act on human meibomian gland epithelial cells and stimulate their lipid accumulation. This azithromycin effect appears to be paralleled by a cellular maturation, a decreased proliferation, and a holocrine-like secretion.

This azithromycin action is quite notable because MGD is thought to be the most common cause of DED. Typically, the meibomian glands produce and release a lipid mixture that promotes the stability and prevents the evaporation of the tear film, thereby playing an essential role in ocular surface health. Conversely, MGD destabilizes the tear film and increases its evaporation. Meibomian gland dysfunction is caused primarily by hyperkeratinization of the terminal duct epithelium and reduced secretion quality, and it leads to cystic dilatation of glandular ducts, acinar cell death, and lipid deficiency. The end result is DED, characterized by a cycle of tear film hyperosmolarity and ocular surface stress and leading to increased friction, inflammation, and damage to the eye. The effect of moderate to severe DED is analogous to conditions such as dialysis and severe angina.
and is associated with significant pain, role limitations, low vitality, and poor general health.5

Given our finding that azithromycin stimulates the function and differentiation of IHMGECs in vitro, it is possible that this antibiotic may prove beneficial as a treatment for MGD and its associated DED in vivo.

Yang Liu, MD
Wendy R. Kam, MS
Juan Ding, PhD
David A. Sullivan, PhD

Author Affiliations: Schepens Eye Research Institute, Massachusetts Eye and Ear, and Harvard Medical School, Boston.

Corresponding Author: Yang Liu, MD, Schepens Eye Research Institute, 20 Staniford St, Boston, MA 02114 (yang.liu@schepens.harvard.edu).


Author Contributions: Dr Liu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Liu, Sullivan.

Acquisition of data: Liu.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: Liu, Sullivan.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Liu, Sullivan.

Obtained funding: Liu, Sullivan.

Administrative, technical, or material support: Kam, Ding.

Study supervision: Liu, Sullivan.

Conflict of Interest Disclosures: Schepens Eye Research Institute is planning to submit a provisional patent based, in part, on the data presented in the article. No other disclosures were reported.

Funding/Support: This work was supported by grant EY05612 from the National Institutes of Health, the Margaret S. Sinon Scholar in Ocular Surface Research Fund, and the Guoxing Yao Research Fund.

Role of the Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.


Optic Neuropathy Due to Biotinidase Deficiency in a 19-Year-Old Man

Biotinidase deficiency is an autosomal recessive condition in which the normal recycling of biotin is deficient. If untreated, infants with biotinidase deficiency will develop neurologic derangements including optic atrophy.1 We describe a case of optic neuropathy due to biotinidase deficiency in a 19-year-old man.

Report of a Case | The patient was identified as having biotinidase deficiency on newborn screening and was provided with appropriate supplementation. However, at approximately age 10 years, supplements were discontinued. At age 19 years, he developed simultaneous bilateral vision loss over several weeks. There were no other neurologic symptoms. Family history was unremarkable. Social history was notable for occasional binge drinking since starting college 2 months prior to onset of symptoms. The patient had visual acuity of 20/70 OD and 20/25 OS; he identified 11 of 14 Ishihara color plates with each eye, the flicker fusion frequency was undetectable in the right eye and 9.5 Hz OS (reference range, >30 Hz), and visual fields showed bilateral cecocentral scotomas with respect of the vertical meridian (Figure 1). The pupils were briskly reactive to light with no relative afferent pupillary defect. There was mild optic disc pallor bilaterally and optical coherence tomography showed atrophy of the papillomacular bundle (Figure 2). Neurologic examination findings were otherwise normal. Findings on magnetic resonance imaging of the brain and orbits with contrast were normal. Biotin levels were un-