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Drusen Ooze: A Novel Hypothesis in Geographic Atrophy

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Purpose: To describe a subgroup of subjects with soft drusen associated with geographic atrophy (GA) and novel spectral-domain OCT (SD-OCT) findings consistent with presumed drusen leakage. We also propose a mechanism leading to GA progression in these patients.

Design: A retrospective, observational cohort study.

Participants: Forty-eight eyes of 33 patients with soft drusen secondary to age-related macular degeneration (AMD).

Methods: Drusen were evaluated with SD-OCT and retinal imaging to characterize the development of atrophy-associated drusen regression (drusen collapse) over a follow-up period of ≥18 months.

Main Outcome Measures: The presence of isoreflective dots at the outer retinal layers associated with retinal pigment epithelium (RPE) defects. Percentages of previously reported hyperreflective RPE, and hyperreflective dots (HRDs) were also determined.

Results: Nineteen of 48 eyes (39.6%) showed a collapse of ≥1 druse during the follow-up period. Thirty-four foci of collapsed drusen were found to be associated with either isoreflective dots associated with RPE defects (32.4%), hyperreflectivity of the RPE (91.2%), or HRDs (79.4%). A post hoc showed the adjusted odds ratio of drusen collapse for isoreflective dots (65.8), for HRDs (6.0) or both (12.1).

Conclusions: In soft drusen progressing to subsequent atrophy, approximately 33% were associated with isoreflective dots and RPE defects. In addition, overlying hyperreflectivity of the RPE and HRDs were noted with high frequency. Presence of isoreflective dots, with or without HRDs, was associated with a strong risk of developing atrophy compared with drusen without these findings. We hypothesize that these isoreflective dots associated with RPE defects may be debris extruded from the soft drusen into the subretinal space, which we have termed "drusen ooze." Drusen ooze may activate the RPE apical surfaces, leading to a marked increase in phagocytosis/endocytosis of extracellular debris that eventually overwhelms the RPE capacity, and leads to RPE death, subsequent release of intracellular RPE material and thereby propagate a cycle of cellular death resulting in GA development and progression. Therapeutic targeting of drusen material, prior to its extrusion into the subretinal space and prior to irreversible damage to the RPE, might prevent or delay onset and progression of GA.

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Phase 1 Trial of Anti–Vascular Endothelial Growth Factor/Antiangiopoietin 2 Bispecific Antibody RG7716 for Neovascular Age-Related Macular Degeneration

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Purpose: RG7716 is a novel bispecific antibody that simultaneously binds vascular endothelial growth factor (VEGF) and another key angiogenic factor, angiopoietin 2. A phase 1 study of intravitreal RG7716 was conducted to evaluate single-dose and multiple-dose safety in patients with neovascular age-related macular degeneration (AMD).

Design: Open-label, single and multiple ascending-dose study.

Participants: Twenty-four patients diagnosed with neovascular AMD with best-corrected visual acuity (BCVA) of 20/40 to 20/400 (Snellen equivalent) and refractory subfoveal choroidal neovascularization defined as leakage on fluorescein angiography or fluid on spectral-domain optical coherence tomography despite 3 or more intravitreal anti-VEGF treatments in the preceding 6 months.

Methods: Single intravitreal doses of 0.5 mg, 1.5 mg, 3 mg, and 6 mg RG7716 were administered in stepwise dose-escalation groups, each with 3 patients. In the multiple-dose phase, 6 patients were enrolled and received 3 treatments each of 3 mg and 6 mg RG7716.

Main Outcome Measures: Safety and tolerability, changes in baseline BCVA, and central subfield thickness (CST).

Results: There were no dose-limiting toxicities in either the single-dose or multiple-dose group. Treatment-emergent ocular adverse events were mild. There was a single withdrawal and 1 serious adverse event, both deemed to be unrelated to the study drug by principal investigators. In the combined single-dose groups and in the 6-mg multiple-dose group, BCVA increased from baseline to 28 days after the last dose administration by a median of 7 letters (range, 0−18 letters; n = 11) and 7.5 letters (range, 3−18 letters; n = 6), respectively. The corresponding median reduction from baseline in CST were 42 μm (range, −101 to 10 μm; n = 11) and −117 μm (range, −252 to −7 μm; n = 6), respectively. After multiple 3-mg RG7716 doses, no changes

were observed in either BCVA (median, −0.5 letters; range, −9 to 8 letters; n = 6) or CST (median, −9 μm; range, −188 to −1 μm; n = 6).

Conclusions: RG7716 was well tolerated and exhibited an overall favorable safety profile, with evidence of improvements in BCVA and anatomic parameters. These data support further evaluation of RG7716 in phase 2 trials.

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OCT-Leakage Mapping: A New Automated Method of OCT Data Analysis to Identify and Locate Abnormal Fluid in Retinal Edema

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Purpose: To test OCT-Leakage, a new method of analyzing and mapping sites of lower optical reflectivity found on OCT, by examining eyes with various types of retinal edema to identify abnormal increases in retinal extracellular fluid.

Design: Prospective analysis of a cohort of cases.

Participants: Healthy eyes and eyes with retinal edema in the setting of different retinal diseases.

Methods: Prospective OCT-Leakage analysis of 12 eyes with various types of retinal edema, such as diabetic macular edema, branch retinal vein occlusion, idiopathic perifoveal telangiectasia, and Irvine-Gass syndrome, representing intraretinal edema and eyes with idiopathic central serous chorioretinopathy and neovascular age-related macular degeneration representing subretinal fluid accumulation, in order to compare with OCT-Leakage analysis of a series of 41 eyes of 24 healthy controls. Raw scan data from the OCT images were exported and used to calculate lower than normal optical reflectivity maps (low optical reflectivity [LOR] ratios). Optical reflectivity LOR maps (OCT-Leakage maps) were collected for the full retina A-scan and layer by layer after segmentation. Low optical reflectivity ratios from patients with the different conditions of retinal edema and controls were compared. Fluorescein angiography (FA) and OCT angiography (OCTA) were performed in all eyes.

Main Outcome Measures: Identification of areas of abnormal retinal fluid accumulation.

Results: The OCT-Leakage maps based on sites of LOR (LOR ratios) delineated the location of intraretinal and subretinal fluid, always integrating the location of the sites on FA and the vascular abnormalities observed on OCTA. The areas of fluid outline in the OCT-Leakage maps were coincident and generally larger than those seen on FA. In all cases, the OCT-Leakage maps were able to identify the location of the fluid in the different segmented retinal layers.

Conclusions: Mapping of lower reflectivity sites within the retina demonstrates the amount and location of retinal and subretinal fluid in different retinal diseases, showing potential to contribute to their management. Furthermore, the possibility of complementarity between OCT-Leakage and OCTA is highly promising.

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Physiologic and Psychologic Risk Factors in Central Serous Chorioretinopathy

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Purpose: Central serous chorioretinopathy (CSCR) is characterized by macular detachment due to thickened choroid, mostly affecting young men under perceived stress. Although most previous studies on CSCR have been retrospective and have focused on a single facet of the patient's personality, we conducted a prospective, intercontinental, controlled study to analyze the multifaceted personality profile in CSCR.

Design: Prospective, cross-sectional, case-control study.

Participants: Subjects with CSCR from 6 university-based eye clinics consented to participate in a questionnaire. Controls without retinal disease were recruited from the same clinics.

Methods: The interview consisted of a 60-item questionnaire. Recruitment of participants was from January 2015 to February 2016. Controls were matched for age, gender, and race. Statistical analyses were performed using univariate and multivariate analyses.

Main Outcome Measures: The main parameters registered were presence of stress, daily number of cups caffeine intake, and personality traits (Type A; obsessive−compulsive; aggressive).

Results: A total of 83 consecutive patients with CSCR (mean age, 45.9 years; male, 80.7%) and 83 controls (mean age, 46.0 years; male, 80.7%) were analyzed for 60 variables. Multivariate analysis revealed a strong association with obsessive−compulsive behavior ($P = 0.001$), caffeine intake ($P = 0.002$), Type A personality ($P = 0.002$), continuous stress ($P = 0.001$), and premature ejaculation ($P = 0.001$).

Conclusions: This study sheds light on the unique psychologic functioning of patients with CSCR: preoccupied, inflexible, perfectionist (obsessive−compulsive tendency), competitive, ambitious, impatient, high achiever (Type A personality), and under continuous stress. In addition, caffeine abuse and premature ejaculation were linked to CSCR.

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The Epidemiology of Stargardt Disease in the United Kingdom

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Purpose: To establish the incidence of Stargardt disease (STGD) in the United Kingdom and define baseline characteristics of newly diagnosed patients.

Design: Prospective epidemiologic study undertaken under the auspices of the British Ophthalmological Surveillance Unit (BOSU).

Participants: New incident cases of STGD in the United Kingdom reported by ophthalmologists to BOSU during a 12-month period, from June 1, 2012, to June 1, 2013.