Investigative Ophthalmology & Visual Science

Re: Trivizki et al. Local Geographic Atrophy Growth Rates Not Influenced by Close Proximity to Non-Exudative Type 1 Macular Neovascularization

We read with great interest the article "Local Geographic Atrophy Growth Rates Not Influenced by Close Proximity to Non-Exudative Type 1 Macular Neovascularization" by Omer Trivizki, Philip J. Rosenfeld, and coworkers.[1] Naturally, we are intrigued by the comparison to our study "Type 1 Choroidal Neovascularization Is Associated with Reduced Localized Progression of Atrophy in Age-Related Macular Degeneration."[2] At first glance, these two studies seem to contradict each other. However, we do not see a strong contradiction, but rather further evidence in their data for a localized protective effect of type 1 macular neovascularization (MNV) on geographic atrophy (GA) progression (cf., "spatially specific hypothesis," as explained below).

In detail, Omer Trivizki et al. examined the impact of non-exudative type 1 MNV on retinal pigment epithelium (RPE) atrophy progression.[1] Based on histopathologic data, it was speculated that type 1 MNV might restore sub-RPE perfusion by bypassing the diseased Bruch's membrane.[3–5] The authors improved upon our[2] and other[6–8] previous analyses by modeling growth trajectories of GA spread and accounting for spatial autocorrelation.[9] Further, the authors decided not to include eyes with RPE atrophy fully embedded within non-exudative type 1 MNV, which may indeed represent a distinct entity.[1] However, there are two critical differences between their and our analysis that ought to be highlighted.

First, Trivizki et al. did not test the hypothesis on the study population level (i.e. *P* values were computed for each eye separately). Moreover, the estimates were not conditioned on the progression rates of a larger natural history study of GA and/or fellow-eye progression rates.[1] In our view, these factors make their analysis conservative.

Second, and more importantly, the hypotheses tested in our manuscript (*H1*) and their manuscript (*H2*) differ fundamentally.[1,2]

- Pfau et al. hypothesis (H1)[2]: Type 1 MNV is associated with a reduced localized progression of RPE-atrophy (i.e. "spatially specific hypothesis").
- Trivizki et al. hypothesis (H2)[1]: Type 1 MNV slows the progression of RPE-atrophy along a spatial gradient (i.e. "halo hypothesis").

Of course, both hypotheses are reasonable. Nevertheless, we consider our initial hypothesis (H1) more appropriate, based on extrapolation from other retinal diseases. Choriocapillaris loss in hypertensive retinopathy typically manifests as well-demarcated RPE atrophy ("Elschnig spots") without marked alterations in the adjacent retina.[10] Vice versa, we expect that enhancement of sub-RPE perfusion affects the overlying RPE primarily, without altering RPE atrophy progression in the adjacent retina. With this framework, demonstrating a continuous spatial gradient (beyond the binary effect of colocalization) would be unnecessary to prove a protective effect of type 1 MNV.

Figures 3, 4, and 5 in the study of Trivizki and coworkers reveal a slower median RPE atrophy progression in the subregion colocalizing with MNV (0 to 0.1 mm subregion) compared to the overall median elsewhere (patients 1, 4, 5, 7, 8, and 9 [i.e. 6 of 9 patients]), supporting our spatially specific hypothesis.[1]

Some patients even support the spatially specific hypothesis, but not the halo hypothesis. For example, patient 7 in Figure 5 shows a spatially specific slower RPE atrophy progression in the area colocalizing with the type 1 MNV lesion, but no spatial gradient across the subregions distant to the type 1 MNV.[1] Thus, the exact choice of hypothesis can determine whether a given observation counts as evidence for or against a protective effect of type 1 MNV.

In conclusion, besides differences in the analysis and patient selection, the precise hypothesis definitions affect the conclusions of both papers. Based on visual inspection of the plots, the data from Trivizki et al. appear to be compatible or even supportive of our original hypothesis of a localized protective effect of type 1 MNV on GA progression.[1,2] Of note, this potential protective effect has major implications for the interpretation of current and the design of future interventional trials in GA. Given the limited number of patients in Trivizki's and our studies, prospective studies of the structural and functional impact of non-exudative type 1 MNV on age-related macular degeneration progression are warranted.

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References

1. Trivizki O, Moult EM, Wang L, et al. Local Geographic Atrophy Growth Rates Not Influenced by Close Proximity to Non-Exudative Type 1 Macular Neovascularization. *Invest Ophthalmol Vis Sci*. 2022;63(1):20.
2. Pfau M, Möller PT, Künzel SH, et al. Type 1 Choroidal Neovascularization Is Associated with Reduced Localized Progression of Atrophy in Age-Related Macular Degeneration. *Ophthalmol Retin*. 2020;4(3):238–248.
3. Chen L, Messinger JD, Sloan KR, et al. Nonexudative Macular Neovascularization Supporting Outer Retina in Age-Related Macular Degeneration: A Clinicopathologic Correlation. *Ophthalmology*. 2020;127:931–947.
4. Grossniklaus HE, Green WR. Choroidal neovascularization. *Am J Ophthalmol*. 2004;137(3):496–503.
5. Chen L, Li M, Messinger JD, Ferrara D, Curcio CA, Freund KB. Recognizing Atrophy and Mixed-Type Neovascularization in Age-Related Macular Degeneration Via Clinicopathologic Correlation. *Transl Vis Sci Technol*. 2020;9(8):8.
6. Capuano V, Miere A, Querques L, et al. Treatment-Naïve Quiescent Choroidal Neovascularization in Geographic Atrophy Secondary to Nonexudative Age-Related Macular Degeneration. *Am J Ophthalmol*. 2017;182:45–55.
7. Dansingani KK, Freund KB. Optical coherence tomography angiography reveals mature, tangled vascular networks in eyes with neovascular age-related macular degeneration showing resistance to geographic atrophy. *Ophthalmic Surg Lasers Imaging Retin*. 2015;46(9):907–912.
8. Christenbury JG, Phasukkijwatana N, Gilani F, Freund KB, Sadda S, Sarraf D. Progression of macular atrophy in eyes with type 1 neovascularization and age-related macular degeneration receiving long-term intravitreal anti-vascular endothelial growth factor therapy: An optical coherence tomographic angiography analysis. *Retina*. 2018;38(7):1276–1288.
9. Moult EM, Shi Y, Zhang Q, et al. Analysis of correlations between local geographic atrophy growth rates and local OCT angiography-measured choriocapillaris flow deficits. *Biomed Opt Express*. 2021;12(7):4573–4595.
10. Hayreh SS, Servais GE, Virdi PS. Fundus Lesions in Malignant Hypertension: VI. Hypertensive Choroidopathy. *Ophthalmology*. 1986;93(11):1383–1400.

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