Intralesional macular atrophy in anti-vascular endothelial growth factor therapy for age-related macular degeneration in the IVAN trial

Response to Letter

We read with interest the letter by Călugăru and Călugăru in response to our paper published in the journal.1

The authors raise the issue of angiographic type at baseline and make some useful points about the complexity of baseline diagnosis. We agree that the interpretation of imaging in nAMD remains challenging. We devoted considerable amounts of time in the setting of our network of reading centres in further developing our classifications from the original ones used in IVAN and CATT (references 1-6 in our article). Contrary to the authors’ statement, we did in fact consider the proportions of classic vs occult choroidal neovascularisation (CNV) at baseline (at least in a categorical manner) as shown in our Table 2. Moreover, we investigated the effect of the proportion of classic CNV at baseline, and the presence of subretinal fluid and pigment epithelial detachment both at baseline and at final visit, in our primary analyses of predictors of the development of macular atrophy (MA) (Figures 3 and 4).

We recognise that there continues to be a significant debate amongst the research and clinical community about the subclassification of polypoidal choroidal vasculopathy (PCV). We did not have access to indocyanine green angiography (ICGA) in the IVAN study. The points about the response to subtypes of treatment are interesting but were outside the scope of our study. However, we are in agreement that ICGA is an important adjunct in the diagnosis in neovascular age-related macular degeneration (nAMD) in the clinic and particularly when PCV is suspected. One study from the UK reported PCV in 9.1% of Caucasian people presenting with nAMD.2  As optical coherence tomography (OCT) angiography becomes increasingly used in clinical practice this may also prove useful in improving the identification of PCV.

The authors comment on the OCT definition of MA. In our study we used OCT as supporting evidence only, requiring the MA to be visible on colour photography or fluorescein angiography. The authors speculate on the possible effects of antiVEGF therapy on the function of the choriocapillaris. We agree that this may prove important but we did not have data to explore this further.

Finally the authors make the point that we “found no significant associations between development of intralesional MA [ILMA] and drug or treatment frequency as well as any other morphologic or visual function measure” and argue that we should have investigated a much wider set of baseline covariatesin our analyses. They list a number of other features visible on current OCT images as potential covariates which we recognise may prove informative in the future. In responding to their statement we have preferred to describe associations with the predictor first and the outcome second and to separate out the associations (i) between drug or treatment frequency or other morphological measure and incident ILMA (Figure 3) from (ii) between visual function and ILMA. With respect to (i), the outcome was binary and so fitting lots of covariates runs the risk of the logistic model not fitting. We restricted covariates in this analysis to a number appropriate for the sample size and for which there was an *a priori* biologically plausible relationship. With respect to (ii), we believe that it is appropriate to adjust only for covariates that are not associated with the development of ILMA. Otherwise, adjustment runs the risk of removing any effect of the groups being compared. In this context, our finding of no association of visual acuity (without adjustment) with ILMA seems robust, since the direction of our hypothesis was that ILMA should reduce visual acuity.

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