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Editorial

To dry or not too dry: should we be more tolerant of stable subretinal fluid in patients receiving anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration?

Since their introduction in 2006, intra-vitreal anti-vascular endothelial growth factor (anti-VEGF) treatments for neovascular age-related macular degeneration (nAMD) have become widely available and increasingly used. Their use has revolutionized visual outcomes, decreased the incidence of legal blindness, improved patient quality of life and reduced the overall public health expenditure that was attributable to the natural history of nAMD.[1,2] Frequent and ongoing treatments, however, pose a substantial burden on patients, caregivers, staff and the healthcare system,[3] and may confer the risk of iatrogenic macular atrophy.[4]

This burden of treatment has created the impetus for clinicians to develop alternative treatment protocols, such as *pro re nata*[5] and treat-and-extend.[6] In an effort to reduce the number and frequency of intravitreal injections, these protocols deviate from the fixed monthly treatments used in the pivotal studies.[7,8] The current *pro re nata* and treat-and-extend regimens still aim to maintain a completely dry retina, with treatment decisions based on the unique disease parameters of individual patients, including retinal features on ocular coherence tomography (OCT) imaging. Given the heterogeneity of nAMD and its response to treatment, the best management approach varies between different patients, and at different stages of their disease.[9] In 2015, how should treating ophthalmologists approach these complex management decisions and on what evidence base?

The past decade of experience has provided additional information to help guide these decisions. Advances in spectral domain ocular coherence tomography (SD-OCT) technology have refined our understanding of relevant biomarkers of disease activity. The ability to distinguish retinal fluid sub-compartments on SD-OCT has allowed clinicians to better individualize therapy, interpret the response to treatment and predict visual recovery. We now understand that not all areas of hypo-reflective signal on OCT reflect fluid accumulation from exudative disease that requires treatment. Rather, they may represent chronic, degenerative changes or potential anatomical spaces.[10] The latest evidence indicates that small volumes of stable sub-retinal fluid (SRF) may be tolerable and even protective in nAMD.[11] This suggests a paradigm shift whereby, in simple terms, 'not all retinal fluid is bad, nor needs to be got rid of'. The implication is that fewer anti-VEGF treatments may be needed for selected patients with nAMD, which could substantially reduce the treatment burden at the population level. But when can treatment safely be withheld, without compromising visual outcome? Several recent studies on the prognostic value of fluid localization in retinal sub-compartments are instructive.

The 'Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration' (EXCITE) study compared ranibizumab dosing regimes in patients with sub-foveal nAMD.[12] Intra-retinal fluid (IRF), also referred to as intra-retinal cysts (IRCs) was found to be significantly associated with lower best-corrected visual acuity (BCVA) at baseline and over 12 months.[13] The study also reported that recurrence of IRC during follow up had no additional negative effect on vision. Conversely, baseline SRF had no effect on visual recovery, whereas recurrence of SRF showed a tendency for an additional negative effect on BCVA ($P = 0.06$).

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Pigment epithelial detachments at baseline also showed a negative influence on visual outcome, but only in combination with IRF and SRF. Central retinal thickness showed a significant correlation with improving BCVA during the loading dose. This became less evident during the maintenance phase, possibly as a result of irreversible damage to the retinal architecture. The integrity of the retinal pigment epithelium (RPE) was not assessed in this trial.

In keeping with these results, the MONT BLANC study showed that IRCs were the strongest anatomical predictor for lowest initial visual acuity (VA) and reduced BCVA gain with anti-VEGF therapy over a follow-up period of 12 months ($P = 0.006$).[14] Baseline pigment epithelial detachment and SRF only demonstrated a negative effect on BCVA when in combination with IRC. Accurate measurements of central retinal thickness failed to predict visual outcomes. The integrity of photoreceptor and RPE layers were not assessed.

A study by Wickremasinghe *et al.* of Australian patients with nAMD found that mean baseline BCVA was significantly worse in eyes with IRF, compared with eyes with SRF alone (20/122 and 20/72, respectively; $P = 0.006$).[15] After three injections, eyes that were dry had better BCVA at 12 months (0.61 [Snellen equivalent 20/80]; 95% confidence interval [CI], 0.52–0.70) compared with those with residual IRF (0.95 [20/180]; 95% CI, 0.78–1.11; $P < 0.05$). Eyes with SRF alone after three injections (0.65 [20/90]; 95% CI, 0.39–0.91) had similar vision to those that were dry. Eyes with persistent SRF at 12 months also had better BCVA when compared with those with a persistent IRF component (20/69 and 20/120, respectively; $P = 0.07$). Eyes with residual SRF alone were similar to those that were dry (20/90). Regardless of the presence of fluid, eyes with RPE hyperreflectivity at baseline were more likely to lose BCVA (48.3% *vs*. 19.7%; $P = 0.006$) and achieve poorer final BCVA (20/155) compared with eyes without hyperreflectance (20/90; $P = 0.02$). Most eyes with persistent fluid after three injections also had persistent fluid at 12 months, suggesting that the ability to dry the retina is determined early in the course of treatment. The presence of pigment epithelial detachment at baseline and after initial injections made no difference to final BCVA.

The negative predictive value of IRF was again demonstrated in the 'Comparison of Age-Related Macular Degeneration Treatments Trial' (CATT).[16] This prospective cohort analysis found that patients with residual IRF had worse mean VA at all time points, irrespective of other retinal morphologic features, anti-VEGF drug and treatment regimen. At 12 months, mean VAs of eyes with foveal, extrafoveal and no IRF were 62.4, 67.2 and 71.2 letters, respectively ($P < 0.001$).

In contrast to IRF, this study found that SRF or sub-RPE fluid at the fovea did not significantly influence BCVA ($P = 0.40$ and $P = 0.051$, respectively). Indeed, at 12 months, eyes with a thin layer of SRF had a mean VA that was 5.3 letters better than eyes without any SRF. There was a bimodal effect of retinal thickness on VA, whereby a retinal thickness of 120–212 μm conferred better VA at all time points than eyes with thicker or thinner retinas. A greater proportion of eyes treated with monthly ranibizumab had abnormal retinal thinning (<120 μm), raising the possibility of iatrogenic neural tissue loss and fibrosis.

There is further evidence that the therapeutic goal of completely drying the macula may pose a risk of iatrogenic macular atrophy. In the CATT and 'VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD' (VIEW) studies, the more frequent monthly injection schedule arm of in studies were both associated with a higher proportion of patients achieving a dry retina.[17,18] This conferred low or modest visual gains, while requiring considerably more treatments (Table 1). In the CATT, patients receiving monthly treatment had a 59% higher risk of GA development ($P = 0.003$) than those receiving *pro re nata* treatment.[4] Treatment with ranibizumab was more effective at drying the retina than bevacizumab and was associated with a 43% higher risk of developing GA than bevacizumab treatment ($P = 0.02$).[17]

The risk of developing GA was also related to the anatomical location of retinal fluid. The presence of IRF on OCT was associated with a doubling of the risk of GA in comparison with no IRF (aHR, 2.10; 95% CI, 1.34–3.31). In contrast, patients with any sub-foveal SRF (>25 μm) had a lesser risk of developing GA.[17]

With regard to the prognostic value of fluid spaces in retinal sub-compartments, a summative assessment of the literature clearly identifies IRF as a negative predictor of visual outcome in nAMD. Cysts at baseline could indicate pre-existing and irreversible retinal damage or a more aggressive form of choroidal neovascularization (CNV), decreasing the response to treatment and visual prognosis.[14] In the EXCITE study, IRF showed the most rapid resolution after treatment and the most rapid recurrence in treatment-free periods.[13] This suggests that IRF represents transient vascular leakage, which responds most sensitively to anti-VEGF therapy. This sensitivity may be explained by the high intra-retinal bioavailability of ranibizumab and the capacity of the neurosensory retina for structural repair. Early IRF, which responds well to anti-VEGF, may be largely due to VEGF-mediated vascular permeability. Late IRF could be related to non-VEGF-mediated mechanisms, such as apoptotic or necrotic cell death.[16]

Table 1. Selected results from CATT[17] and VIEW[18] studies

CATT (2 years)	Ranibizumab 0.5q4	Bevacizumab 1.25q4	Ranibizumab 0.5 PRN	Bevacizumab 1.25 PRN
Mean number of treatments	22.4	23.4	12.6	14.1
Patients with no fluid on OCT (%)	45.5	30.2	22.3	13.9
Patients gaining ≥15 letters (%)	32.8	31.8	30.7	28.3
Mean change in BCVA	8.8	7.8	6.7	5.0

VIEW 2 (1 years)	Ranibizumab	Aflibercept		
	0.5q4	2q4	0.5q4	2q8
Mean number of treatments		12.2–12.4		7.5
Patients with no fluid on OCT (%)	60.4	80.3	63.9	71.9
Patients gaining ≥15 letters (%)	34	29.4	34.8	31.4
Mean change in BCVA	9.4	7.6	9.7	8.9

0.5q4 = 0.5 mg monthly; 1.25q4 = 1.25 mg monthly; 0.5PRN = 0.5 mg as needed; 2q4 = 2.0 mg monthly; 2q8 = 2 mg every 2 months after 3 monthly doses. BCVA, best-corrected visual acuity; CATT, Comparison of Age-Related Macular Degeneration Treatments Trial; OCT, ocular coherence tomography; PRN, *pro re nata*; VIEW, VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD.

In contrast to IRF, a small residual volume of SRF can be tolerated and may indeed benefit the patient. We hypothesize that stable SRF in some patients is not a result of ongoing neovascular activity, but rather a residual anatomical space created by the failure of the neurosensory retina to remain attached or to re-attach to the RPE after complications of nAMD. In many patients, allowing a small amount of persistent SRF (or indeed a persistent, subretinal hyporeflective anatomical space on OCT) is likely to have minimal negative effects on vision, but would greatly reduce the frequency and numbers of injections given. Because VEGF is important in the normal function of the retina, choriocapillaris and RPE, excessive blocking of VEGF could affect the onset and growth of GA. The presence of SRF between the retina and choriocapillaris may possibly protect against the development of GA as well.[11,16] The imperative is therefore to develop an evidence-based protocol to test this hypothesis.

To investigate whether a small amount of SRF can be tolerated with no adverse effects on visual outcome, an Australian Phase IV, 2-year, multicenter randomized controlled trial has commenced. Called the 'FLUID' study, this trial of 347 treatment-naïve patients with nAMD compares a treat-and-extend protocol of ranibizumab (0.5 mg) that allows extension with incomplete resolution of SRF (<200 μm at foveal centre) (Fig. 1), relative to one that requires complete resolution of all retinal fluid. The primary endpoint is mean change in BCVA from baseline to 24 months. The trial is being conducted at 17 sites across 5 states in Australia and was fully enrolled in March 2015 (https://ClinicalTrials.gov; Identifier NCT01972789).

The need remains to efficiently tailor therapy for individual patients with varying responses to anti-VEGF therapies. While central retinal thickness was a traditional biomarker for guiding retreatment in the initial clinical trials and early clinical practice, interpretation of fluid in retinal sub-compartments on SD-OCT offers superior prognostic value and is now routinely assessed. Collective experience with interpreting SD-OCT features in nAMD has identified other anatomical changes that do not represent retinal fluid, but are likely to influence visual response. New entities such as sub-retinal hyperreflective material[19] as well as the integrity of the ellipsoid zone, interdigitation zone and RPE layer all require scrutiny when assessing response to treatment and making re-treatment decisions.

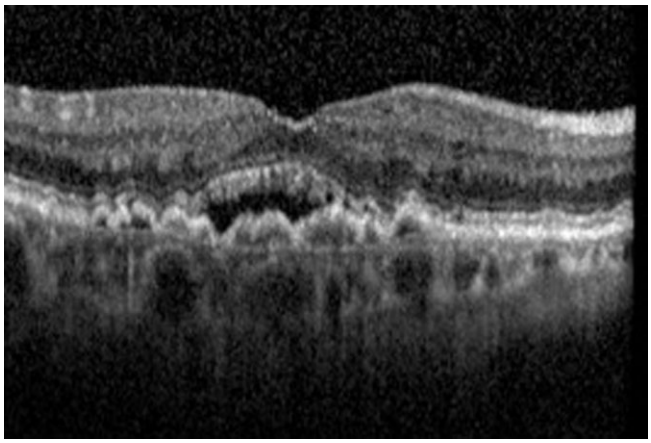

Figure 1. Spectral domain OCT demonstrating subretinal fluid measuring <200 μm at the foveal centre.

Early aggressive treatment of nAMD in an attempt to quickly resolve all retinal fluid seems appropriate, but the challenge comes during follow up. Here, the ongoing neovascular activity of a lesion is inferred by the presence of hyporeflective spaces on OCT. The interpretation of these spaces is often intuitive and based on the ophthalmologists' clinical experience. Which IRCs represent CNV activity and which are

degenerative changes that will not respond to anti-VEGF treatment? Does a hypo-reflective sub-retinal space represent true SRF, draping of the neurosensory retina over drusen, or failure of photoreceptors to re-attach to the unhealthy RPE? Clearly, we still have much to learn. The FLUID study aims to further our understanding of the influence of residual sub-foveal SRF and, as such, to help inform novel therapeutic protocols that ensure the best outcome for every patient with nAMD.

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