Intravitreal Injection of Lucentis and the Vitreomacular Relationship in Patients with Exudative AMD: A Prospective Study

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Purpose: This study aimed to investigate the relationship between intravitreal injections of Lucentis and the vitreomacular surface.

Material and Methods: Central macular thickness (CMT), LogMAR visual acuity and the presence or absence of posterior vitreous detachment (PVD) were noted in Lucentis eligible patients before commencing treatment, and 6 months after initial treatment prospectively. The paired sample t-test repeated measures ANOVA were used.

Results: Of 52 eyes analyzed, 70% were noted to have no PVD prior to injection. Of these, 55% of eyes developed PVD. Comparison of the change in CMT between PVD-induced eyes and pre-existing PVD eyes was statistically significant. PVD induction during treatment was associated with a greater reduction in CMT than in eyes with pre-existing PVD.

Conclusions: The induction of PVD may have an effect on CMT in eyes injected with Lucentis, implying a potential therapeutic effect of PVD in exudative AMD.

Key words: Macular, Neovascularization, Age related macular degeneration, Lucentis

Age-related macular degeneration (AMD) is the largest cause of blind registration in the western world. Although clinically, both dry (atrophic) and exudative forms of AMD are recognized, it is the choroidal neovascular membrane (CNV) that has been the focus of intensive research into agents which stabilize the disease process in what was previously an untreatable condition. There have been considerable advances in treatment of CNV over recent years, with the recent addition of anti-vascular endothelial growth factor (anti-VEGF) agents to the armamentarium.1,2 Much, however, remains obscure regarding the etiology of the disease. Hereditary, inflammatory, degenerative and vascular factors have all been widely implicated, but clearly it represents a multifactorial disease.3

Posterior Vitreous Detachment (PVD) describes the process of separation of the posterior hyaloid face of the vitreous from its attachments to the retina, notably around the optic disc and macula primarily. In humans this is a normal ageing process due to progressive liquefaction of the gel structure. There is an increasing incidence of PVD with age4. In some patients, such as those with diabetes, there are abnormally strong attachments, preventing complete PVD from occurring and resulting in persistent vitreoretinal traction.

There is evidence from animal studies that experimental induction of PVD using intravitreal injection of microplasmin improves vitreous cavity, and therefore possibly inner retinal oxygenation5 and there are numerous clinical reports of reduced macular thickness in cases of macular oedema, after both vitrectomy and enzymatic vitreolysis.6-9

Vitreoretinal adhesion in diabetic retinopathy is believed to promote angiogenesis10 and its role in the pathogenesis of AMD disease is being studied with
increasing interest. Several studies have demonstrated that PVD is less prevalent in eyes with AMD. Krebs et al demonstrated, in a prospective study, that less than half of patients with CNV had PVD development when compared to age-matched controls, or fellow eyes. Furthermore, a study of the role of vitrectomy for AMD with vitreous hemorrhage has shown a reduction in CNV activity after pars plana vitrectomy, indicating the importance of vitreomacular traction in the pathophysiology of CNV in age-related macular degeneration.

The major treatment for exudative AMD involves sequential injection of small volumes of anti-VEGF agent into the vitreous cavity. The effect of this treatment has shown significant improvement, both in terms of lesion characteristics and visual acuity. There is little data relating to the injection of a fluid bolus into the vitreous cavity, on the state of the posterior hyaloid. As AMD treatment involves three or more sequential monthly injections, it is conceivable that PVD development occurs in these patients and thus contributes to the anatomical and visual results.

Macular complications due to peri-foveal vitreous detachment has been documented in literature.

We aimed to investigate the relationship between Lucentis injections & vitreomacular interface by analyzing the incidence of PVD in patients undergoing Lucentis treatment for AMD and how this correlated to the clinical outcomes of visual acuity and optical coherence tomography (OCT) i.e. central macular thickness (CMT).

MATERIAL AND METHODS

After obtaining research and ethics (REC) approval we devised a prospective non-interventional study of patients undergoing intravitreal Lucentis injection for AMD for 6 months.

B - Scan ultrasonography (HiScan, Optikon, Alcon) and Optical Coherence Tomography (OCT) (Time domain: Zeiss Stratus) were performed on consecutive patients listed for Lucentis treatment for exudative macular degeneration in AMD clinics at the Hull & East Yorkshire eye hospital, initially before commencing treatment, and then after 6 months of follow-up. PVD was recorded as present or absent on each occasion.

Central macular thickness (CMT) was taken as the central 1mm scan on a Fast Macular scan when accurate linear delineation by the OCT of inner and outer retinal boundaries was demonstrated. Patients were initiated with Lucentis monotherapy with three initial monthly loading doses followed by an OCT driven prn regime. Best-corrected ETDRS LogMAR acuities were recorded monthly.

The main inclusion criterion was patients with active wet AMD as per current NICE criterion (i.e. evidence of wet AMD worsening, best corrected visual acuity between 6/12 to 6/96 & no permanent damage to fovea/less than 12 disc diameter involvement), treated with intravitreal Lucentis.

Patients with co-existent diabetic retinopathy, those with OCT evidence of vitreomacular traction or high refractive error (less than 4 or more than +4 Dioptres) were excluded from the study, as were patients with OCT evidence of vitreomacular traction.

The main outcome measures were the percentage of eyes with PVD prior to the commencement of treatment with intravitreal Lucentis, and the percentage of eyes which developed PVD during treatment, based on clinical examination, B-scan ultrasonography and OCT. The visual and anatomical outcomes of both PVD and non-PVD eyes were measured by LogMAR visual acuity and CMT respectively.

The study was commenced following the local Research Ethics Approval (REC) and adhered to the tenets of the Declaration of Helsinki.

Visual acuity was measured using the number of ETDRS letters seen, and comparisons made using the paired sample t-test. Macular thickness was quantified using OCT data and analyzed using the paired sample t-test.

A repeated measures ANOVA was used to examine the effects over time of the PVD development on LogMAR acuity and CMT.

RESULTS

Fifty-two eyes were analyzed. The age range was 63-99 years (mean age 76, SD 7 years). 36/52 (70%) were noted to have PVD absent at the time of enrolment. 16/52 (30%) eyes had PVD at enrolment. 23 (44%) were left eyes and 29 (56%) were right eyes. The most prevalent type of CNV was Occult which accounts for 57.5% of cases (n = 30). The remaining cases were Classic 8% (n = 4), Predominantly Classic 17% (n = 9), Minimally Classic 13.5% (n = 7). Two cases were unclassified.
The differences in VA and CMT between the two groups at baseline were evaluated and did not reach statistical significance. 36 cases had no PVD at enrolment. One patient died prior to their follow up. Of the 35 remaining cases with an absent PVD at enrolment, 19 cases (54%) developed PVD whilst 16 cases (46%) did not develop PVD after intra-vitreal injections. Of the 22 fellow non-injected eyes with no PVD at enrolment, 2 (9%) developed PVD during the course of the study on the basis of OCT data although these eyes did not undergo B-scan ultrasonography.

LogMAR visual acuity prior to intravitreal injection was 24 – 76 letters (mean 52 letters), compared with 4 – 81 (mean 50 letters) 6 months post injection. The number of injections administered over the 6 months ranged from 3 – 6 (mean 4.1) and there was no significant difference in the number of injections between groups.

A paired sample t-test was used to compare the VA and OCT CMT scores pre and post intravitreal injection for each individual in the group as a whole.

There was a significant reduction in OCT CMT between the pre and post measures for all patients, \( t(49) = 4.6 \ p < 0.001 \) (Table 1). A significant reduction in OCT CMT (Table 2) was also noted for eyes where a PVD was induced during the study \( (n=19, \text{mean CMT change} = -165) \ t(18) = 4.5, \ p < 0.001 \).

A repeated measure ANOVA was used to examine the effects over time of the PVD first on VA and OCT CMT (figures 1a and b). The patients were assigned to one of 3 groups: those who had PVD at enrolment, those who developed a PVD and those who do not have a PVD.

A series of paired sample t-tests were used to examine the differences between baseline and 6 month follow up measures of VA and OCT CMT in patients who developed PVD. There was a significant difference in OCT CMT post intravitreal injection Fig. 1: Repeated measure ANOVA showing the effects over time of PVD on 1a. VA and 1b. OCT CMT: compared with pre-injection.

These results indicate that the reduction in CMT after PVD induction is significant. The reduction in CMT in patients with PVD present at enrolment and in those who did not develop a PVD did not reach statistical significance.

Although patients with PVD induction during the course of treatment show a slight trend towards better VA (49.4 to 52.1=+2.74 logMAR letters), the overall differences pre- and post-injection were not significant. Overall visual acuity post treatment was

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**Table 1:** Overall reduction in CMT and change in vision pre and post injection treatments.

<table>
<thead>
<tr>
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<th>Pre Injection</th>
<th>6 Months Post-injection</th>
<th>Change</th>
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<tbody>
<tr>
<td>VA (LogMAR)</td>
<td>52.2</td>
<td>50.8</td>
<td>-1.4 (NS)</td>
</tr>
<tr>
<td>OCT CMT (µm)</td>
<td>314</td>
<td>209</td>
<td>-105*</td>
</tr>
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**Table 2:** Overall CMT comparison pre and post injection treatments in relation to PVD.

<table>
<thead>
<tr>
<th>Mean Scores</th>
<th>OCT (pre)</th>
<th>OCT (6 Months Post)</th>
<th>Change</th>
</tr>
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<tbody>
<tr>
<td>PVD at enrolment</td>
<td>281.1</td>
<td>202.6</td>
<td>-78.5 (NS)</td>
</tr>
<tr>
<td>Developed PVD</td>
<td>357.9</td>
<td>193.3</td>
<td>-165.4*</td>
</tr>
<tr>
<td>No PVD</td>
<td>298.4</td>
<td>235.9</td>
<td>-62.5 (NS)</td>
</tr>
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reduced slightly by 1.4 logMAR letters amongst all groups this was not statistically significant.

DISCUSSION
Studies show that the incidence of PVD is lower in patients with exudative AMD and that persistent attachment of the vitreous cortex to the macula may be an additional risk factor in its development. Furthermore, VMT is associated with greater severity of AMD and operated eyes show a reduction in CMT and improvement in best corrected visual acuity following vitrectomy. There is also a demonstrated treatment effect of PPV in CNV regression in eyes without a pre-existing PVD.

In our study, PVD induction was common after repeated intravitreal injection. Although not formally compared, the apparent low level of PVD induction in untreated fellow eyes would seem to suggest a possible effect of the intravitreal injection on the state of the vitreous gel, either related to the fluid bolus, or the anti-VEGF agent itself. There was a significant reduction in CMT when PVD was induced during the course of treatment with intravitreal injections. Interestingly, this was also true of patients that did not develop a PVD at any point (see Table 2) whereas the pre-existing PVD group did not demonstrate a significant reduction in CMT. Although it is difficult to draw conclusions from such small subgroups, it does raise the possibility that there may be a differing pathophysiology of AMD and its response to anti-VEGF agents depending upon the state of the posterior hyaloid.

The category with induced PVD fared slightly better from the point of view of improvement in visual acuity (49.4 to 52.1 = +2.74 logMAR letters) although the difference was not statistically significant. There was no significant difference in the number of injections administered to each of the three groups.

This study does have some limitations. The numbers were relatively small, and the results should therefore be interpreted with some caution. A larger data set would be required to definitively draw conclusions. Additionally, the use of age-matched controls would be useful in further assessing the development of PVD spontaneously without intervention. Visual acuity outcomes may be subject to other variables, including developing cataract. Also, the response to Lucentis in patients with wet AMD is now known to be influenced by genotype. Another reason for this slight decrease in overall mean VA could be the wide variation of VA at presentation & the extent of damage on the fovea prior to treatment as well as treatment failures, our study does not take account of these variables.

Multiple intravitreal injections may hasten PVD development. The relationship between the state of the posterior hyaloid and the change in CMT in our study suggests that the state of the posterior hyaloid, whether attached, or in the process of detaching, may have an impact on the effect of anti-VEGF therapy.

CONCLUSION
Thus in conclusion it is possible that once a PVD has been induced, the course of a patient’s AMD might fare better. Further studies to investigate the therapeutic role of vitrectomy & PVD in wet AMD are warranted.

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REFERENCES