A retrospective study of the influence of the vitreomacular interface on macular oedema secondary to retinal vein occlusion

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ABSTRACT

Aims To compare anti-vascular endothelial growth factor (VEGF) treatment outcomes for macular oedema (ME) secondary to retinal vein occlusion (RVO) based on vitreoretinal interface (VRI) status.

Methods This retrospective case series includes treatment-naive eyes diagnosed with RVO and treated with anti-VEGF injections. Eyes were stratified based on international VRI classification schema at baseline into three groups—vitreomacular traction (group A), no posterior vitreous detachment (PVD) (group B) and PVD without vitreomacular attachment (group C). Fifty-two eyes were identified based on inclusion/exclusion criteria. The primary endpoint was change in central subfield thickness (CST) on optical coherence tomography at 6 months.

Results There were no statistically significant differences in baseline characteristics of patients with RVO when stratified by VRI subgroups. After 6 months of treatment, there was no statistically significant difference in the change in CST from baseline between VRI cohorts (p=0.11). There was a trend demonstrating the greatest improvement in CST in eyes in group A compared with eyes in groups B and C (−224.13 µm, −160.88 µm and −50.92 µm, respectively, p=0.11 between cohorts). Mean change in logarithm of the minimum angle of resolution visual acuity from baseline to month 6 in group A compared with groups B and C was −0.25, −0.14 and −0.13, respectively (p=0.64 between cohorts).

Conclusions We did not identify an association between VRI status and treatment outcomes with anti-VEGF agents for ME secondary to RVO.

INTRODUCTION

Retinal vein occlusion (RVO) is a common retinal vascular disease that affects 1–2% of patients over the age of 40 and 16 million patients worldwide.[1] Though the disease is characterised by blockage of either the central retinal vein or its branches, most vision loss in patients with RVO results from macular oedema (ME).[1] Although the exact mechanism for the development of ME in eyes with RVO is unknown, it is widely accepted that inflammatory factors such as vascular endothelial growth factor (VEGF), cytokines and chemokines are the root cause of the ME that subsequently develops.[2–4] Studies conducted by Noma *et al* found that vitreous levels of VEGF and interleukin (IL)-6 specifically were significantly higher in patients with ME secondary to branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) than in controls, suggesting a plausible role for vitreous inflammatory mediators in the pathogenesis of ME in RVO.[5–7] Contributing factors may include retinal ischaemia (which induces the production of cytokines in the occluded region affected by anoxia), damage to endothelial cells and subsequent impairment of the blood–retinal barrier and increased rigidity of a crossing artery causing compression of the underlying vein.[8] Likewise, another proposed explanation is that RVO results in vitreoretinal adhesion and traction on the retina leading to vascular leakage and subsequently ME.[9]

Previous studies conducted prior to the advent of optical coherence tomography (OCT) have evaluated the role of the vitreoretinal interface (VRI) in treatment outcomes for RVO.[7 10 11] While the vitreous is initially attached to the retina in its entirety, ageing results in the weakening of vitreoretinal adhesion and subsequently a progressive separation; this detachment typically begins in the macula but can progress through various stages of attachment before a total posterior vitreous detachment (PVD) occurs. A 1984 study conducted by Hikichi *et al*[7] showed that in non-ischemic eyes with RVO the prevalence of posterior vitreous adhesion defined by clinical exam was significantly higher in patients with persistent ME than in those without. Similarly, a study conducted by Kado *et al*[10] on central RVO in 1990 observed a lower incidence of ME in eyes with PVD than in eyes without vitreous separation from the macula again using clinical examination techniques to separate patients. A subsequent study done by Avunduk *et al*[11] in 1997 indicated that a total PVD reduced the incidence and persistence of both retinal neovascularization and ME in eyes with RVO. These studies provide precedence in investigating the use of modern clinical diagnostics and treatments that could induce PVD to inhibit persistent ME secondary to RVO.[12 13]

The aim of this retrospective analysis is to approximate whether there is a significant difference in treatment outcomes for ME secondary to RVO when considering patients' VRI status at baseline in the modern era of OCT and anti-VEGF treatment.

MATERIALS AND METHODS

Institutional Review Board approval was obtained from the Cleveland Clinic for this retrospective study. Because of the retrospective nature of the study, written informed consent was not required. Patients were seen at the Cole Eye Institute between January 2011 and June 2014. All study-related

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procedures were performed in accordance with best practices and adhered to the Health Insurance Portability and Accountability Act. Patients were included in the record review if they met the following criteria: (1) a new diagnosis based on the International Classification of Diseases, ninth revision codes of central/hemiretinal, or branch vein occlusion (362.35 or 362.36), (2) the completion of an spectral domain OCT (SD-OCT) at the time of the initial exam and (3) 18 years of age or older. Exclusion criteria included patients who had been referred to or seen at Cole Eye Institute with an existing diagnosis of RVO, patients who had been treated in any capacity for RVO, any prior intravitreal injection treatment, uncontrolled glaucoma, presence of proliferative retinopathy, presence of epiretinal membrane based on review of medical records and OCT, neovascular age-related macular degeneration, history of retinal detachment, prior vitrectomy or prior injection of a vitreolysis agent.

The international classification system of VRI disorders was used to grade the initial OCT findings (Zeiss Cirrus SDOCT, V.6.0, Carl Zeiss Meditech, Dublin, California, USA).[14] Two independent graders reviewed the entire cube scan of the OCT; any discrepancy was resolved by a third reviewer. Patient eyes were sorted into the following groups: vitreomacular traction (VMT) (group A), no PVD (group B) and PVD without vitreomacular attachment (VMA) (group C). VMA, as defined by the classification scheme, was identified based on perifoveal vitreous cortex detachment from the retinal surface, macular attachment of the vitreous cortex within a 3 mm radius of the fovea and no detectable change in foveal contour or underlying retinal tissues.[14] VMT (group A) was also identified based on the classification definition of perifoveal vitreous cortex detachment from the retinal surface, macular attachment of the vitreous cortex within a 3 mm radius of the fovea and association of attachment with distortion of the foveal surface, intraretinal structural changes and/or elevation of the fovea above the retinal pigment epithelium, without a full-thickness interruption of retinal layers (eg, macular hole).[14] A complete PVD was not explicitly defined in the classification schema but was described as a complete separation of the vitreous from the macula and optic nerve. Given this definition, diagnosis of complete PVD would be impossible based on OCT macular cube scans alone; as such, patient eyes were grouped into a 'PVD without VMA' group (group C) if they had a clinical diagnosis of PVD and absence of VMA or VMT on OCT. Eyes were assumed to have a complete vitreoretinal adhesion, labelled in this study as 'no PVD' (group B) if they had no evidence of vitreous detachment on exam or OCT defined as increased reflectivity of the hyaloid visible on the inner retinal surface.[14]

A total of 114 eyes were identified and divided into the following initial groups: no PVD (n=61), PVD without VMA (n=25), VMA (n=7) and VMT (n=21), determined by analysis of OCT recorded at baseline. Of the 114 initial patients that qualified for record review, 52 patients met the entry criteria for treatment analysis that included the following: concurrent diagnosis of ME defined by a central subfield thickness (CST) >300 µm, baseline visual acuity (VA) between 20/20 and 20/400 and treatment with anti-VEGF injection at baseline. No patient with VMA met entry criteria for the analysis. The treatment protocol was determined by retina specialists at a single institute based on comprehensive ophthalmic examination and OCT findings (Zeiss Cirrus SDOCT, V.6.0). Baseline demographics and clinical variables including Snellen VA and OCT parameters were recorded. SD-OCT parameters including CST, cube volume (CV), cube average thickness (CAT) and presence of cystoid ME were also documented from visits corresponding closest to 3 and 6 months.

Snellen VA measurements were converted to logarithm of the minimum angle of resolution (logMAR) values for statistical analysis. Pearson's χ^2 and analysis of variance (ANOVA) tests were used to compare baseline characteristics between groups. Treatment analysis was conducted to assess clinical and anatomical differences in treatment outcomes for ME secondary to RVO based on vitreoretinal status at baseline. Statistical analyses included the conduction of t-tests and ANOVA to compare VA and OCT parameters between cohorts; a 0.05 significance level was assumed.

RESULTS

Baseline characteristics and comparisons

Fifty-two eyes met the entry criteria for treatment analysis and were divided into the following groups: VMT (n=15) (group A), no PVD (n=24) (group B) and PVD without VMA (n=13) (group C). Table 1 summarises the baseline characteristics of patients who met the inclusion criteria for treatment analysis, as defined in the 'Materials and methods' section. The mean age at baseline was 70.3±12.8 years and 57.7% (n=30) were male. The mean baseline logMAR VA was 0.64 (SD=0.37; Snellen equivalent of 20/87) and the mean CST at baseline was 483.0 ±179.9 µm. The average follow-up at 6 months was 174.14 ±20.29 days for group A, 176.52±13.32 days for group B and 181.50±18.07 days for group C. Because of the need for the initial presence of ME, no patients with VMA met the inclusion for treatment analysis as patients with VMA and foveal cystoid ME were categorised as VMT by the international classification of VRI. There were also no patients in the VMT group at baseline that switched groups to VMA following treatment, suggesting alterations in the foveal architecture in the VMT group were largely due to VRI status and not due to ME from RVO.

When comparing baseline demographics across groups stratified by VRI status, patients in group A were significantly more likely to be phakic than those in group B (p=0.027). There were no significant differences between cohorts when considering age (p=0.16), sex (p=0.89) and laterality (p=0.24). Similarly, no significant differences in RVO subtype (hemiretinal vein occlusion, BRVO, CRVO) between groups were present (p=0.73). Baseline measures including logMAR best-corrected visual acuity (BCVA) and OCT parameters were also compared among groups; no significant differences were observed (table 1).

Clinical and anatomic treatment outcomes

Improvement in BCVA from baseline to month 6 was statistically similar for patients irrespective of vitreoretinal status (figure 1; p=0.64 between groups). Only patients in group A made significant improvements in vision at all time points (p=0.009 at 3 months; p=0.013 at 6 months). Final vision at 6 months was statistically similar between cohorts (Snellen equivalent: 20/41, 20/56, 20/71, in groups A, B and C, respectively; p=0.22 between cohorts).

Reduction of CST from baseline to 6 months was comparable between groups despite differences in vitreoretinal status (figure 2; p=0.11). Group A showed the trend with the greatest reduction in CST (baseline to month 6: −224.13 µm, p=0.005). Final CST at 6 months was statistically similar between cohorts (CST: 306.21 µm, 327.39 µm, and 328.25 µm in the group A, B and C cohorts, respectively; p=0.80 between cohorts).

Reductions in CV and CAT were similarly commensurate between cohorts irrespective of vitreoretinal status (p=0.78 and 0.77, respectively). There was no statistically significant