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Vitrectomy as an Adjunct to Treat-and-Extend Anti-VEGF Injections for Diabetic Macular Edema

The Vitrectomy in Diabetic Macular Oedema (VIDEO) Randomized Clinical Trial

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IMPORTANCE There are reported benefits from vitrectomy for diabetic macular edema (DME); however, data precede anti–vascular endothelial growth therapy (VEGF) therapy, supporting a need to assess the current role of vitrectomy.

OBJECTIVE To determine rates of recruitment and efficacy outcomes of vitrectomy plus internal limiting membrane (ILM) peeling adjunctive to treat-and-extend (T&E) anti-VEGF injections for diabetic macular edema (DME).

DESIGN, SETTING, AND PARTICIPANTS This was a single-masked, multicenter randomized clinical trial at 21 sites in the United Kingdom from June 2018 to January 2021, evaluating single eyes of treatment-naive patients with symptomatic vision loss from DME for less than 1 year. Inclusion criteria were best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study letter score greater than 35 (approximate Snellen equivalent, 20/200 or better) and central subfield thickness (CST) greater than 350 µm after 3 monthly intravitreal injections of ranibizumab or aflibercept. Data analysis was performed in July 2023.

INTERVENTIONS Patients were randomized 1:1 into vitrectomy plus standard care or standard care alone and further stratified into groups with vs without vitreomacular interface abnormality. Both groups received a T&E anti-VEGF injection regimen with aflibercept, 2 mg, or ranibizumab, 0.5 mg. The vitrectomy group additionally underwent pars plana vitrectomy with epiretinal membrane or ILM peel within 1 month of randomization.

MAIN OUTCOMES AND MEASURES Rate of recruitment and distance BCVA. Secondary outcome measures were CST, change in BCVA and CST, number of injections, rate of completed follow-up, and withdrawal rate.

RESULTS Over 32 months, 47 of a planned 100 patients were enrolled; 42 (89%; mean [SD] age, 63 [11] years; 26 [62%] male) completed 12-month follow-up visits. Baseline characteristics appeared comparable between the control (n = 23; mean [SD] age, 66 [10] years) and vitrectomy (n = 24; mean [SD] age, 62 [12] years) groups. No difference in 12-month BCVA was noted between groups, with a 12-month median (IQR) BCVA letter score of 73 (65-77) letters (Snellen equivalent, 20/40) in the control group vs 77 (67-81) letters (Snellen equivalent, 20/32) in the vitrectomy group (difference, 4 letters; 95% CI, −8 to 2; *P* = .24). There was no difference in BCVA change from baseline (median [IQR], −1 [−3 to 2] letters for the control group vs −2 [−8 to 2] letters for the vitrectomy group; difference, 1 letter; 95% CI, −5 to 7; *P* = .85). No difference was found in CST changes (median [IQR], −94 [−122 to 9] µm for the control group vs −32 [−48 to 25] µm for the vitrectomy group; difference, 62 µm; 95% CI, −110 to 11; *P* = .11).

CONCLUSIONS AND RELEVANCE Enrollment goals could not be attained. However, with 47 participants, evidence did not support a clinical benefit of vitrectomy plus ILM peeling as an adjunct to a T&E regimen of anti-VEGF therapy for DME.

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Visual Abstract

Supplemental content

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There are reported potential benefits from vitrectomy for diabetic macular edema (DME).[1] However, systematic interpretation of the literature on vitrectomy for DME is problematic due to variable inclusion criteria, outcome measures, and follow-up regimens. The potential development of either postvitrectomy or corticosteroid-induced secondary cataract is a frequent potential confounder, as is vitreomacular interface abnormality (VMIA).[2-4] Most of these data arise from the era preceding anti-vascular endothelial growth factor (VEGF) therapy, the introduction of which has improved visual outcomes for DME.[5]

Despite these caveats, studies[3,4,6-15] have reported that vitrectomy, usually including induction of a posterior vitreous detachment (PVD) and peeling of the internal limiting membrane (ILM), is effective in reducing DME and more effective than laser treatment for reducing central subfield thickness (CST). More recent retrospective data from uncontrolled studies of treatment-naive patients with center-involving DME have suggested that vitrectomy and ILM peeling alone may be effective for improving visual acuity (VA) and macular thickness.[6,8]

The Vitrectomy in Diabetic Macular Oedema (VIDEO) randomized clinical trial (RCT) was designed as a randomized pilot clinical trial. The aims of this study were to assess whether a definitive trial was feasible, to determine whether there was sufficient evidence of clinical effect to justify a definitive trial, and, if so, to inform the design and power of that study. The specific hypothesis being tested was that vitrectomy would be an effective adjunct to standard care, a treat-and-extend (T&E) regimen of anti-VEGF injections. The patient population included individuals with persistent center-involving DME despite 3 previous anti-VEGF injections.

Key Points

Question What were the rates of recruitment and efficacy outcomes of vitrectomy plus internal limiting membrane (ILM) peeling adjunctive to a treat-and-extend anti–vascular endothelial growth factor (VEGF) injection regimen for diabetic macular edema (DME)?

Findings In a randomized clinical trial, only 47 of 100 patients were enrolled over 32 months. No differences in best-corrected visual acuity, central subfield thickness, or change in these parameters from baseline to 12 months was found between groups.

Meaning Enrollment goals were not met, but no evidence of benefit on visual or anatomic outcomes were noted when adding vitrectomy with ILM peeling to a treat-and-extend anti-VEGF therapy for DME.

Methods

The VIDEO RCT was a pragmatic, stratified, single-masked, multicenter randomized pilot clinical trial with 12 months of follow-up conducted at 21 National Health Service sites in the United Kingdom from June 2018 to January 2021. The study adhered to the tenets of the Declaration of Helsinki and received ethics approval from the London-Brent Research Ethics Committee prior to recruitment. The trial report followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. Written informed consent was obtained from all participants. No compensation or incentives were offered to participants. Data analysis was performed in July 2023.

The key features of the protocol (Supplement 1) are summarized here and in **Figure 1**. Trial eligibility criteria included being treatment naive and having symptomatic vision loss from DME for less than 1 year, baseline best-corrected VA (BCVA) better than an Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 35 (Snellen equivalent of 20/200), thickness response to anti-VEGF therapy, and CST persistently greater than 350 µm after 3 monthly intravitreal injections of ranibizumab or aflibercept. Where 2 eyes of a participant met the inclusion criteria, the worse eye based on BCVA and CST was selected. Systemic criteria included having type 1 or type 2 diabetes, being aged 18 years or older, and having capacity to give informed consent.

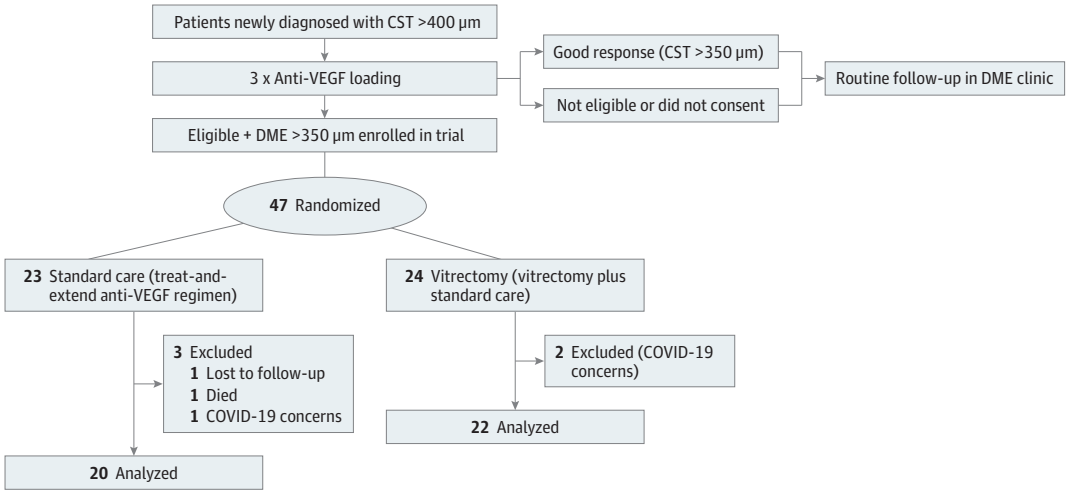
Both groups received T&E anti-VEGF injection therapy with either aflibercept, 2 mg, or ranibizumab, 0.5 mg. The T&E protocol is described here and outlined in the eFigure in Supplement 2. The control group underwent a T&E intravitreal injection regimen of aflibercept, 2 mg, or ranibizumab, 0.5 mg. The intervention (vitrectomy) group additionally underwent pars plana vitrectomy at a gauge of the surgeon's choice, with induction of a PVD, and epiretinal membrane (ERM) or ILM peeling facilitated by vital staining. Panretinal photocoagulation laser treatment was permitted at the investigator's discretion. Surgery was performed within 1 month of randomization.

Primary outcome measures were rate of recruitment and distance BCVA. Secondary outcome measures were CST at month 12, change in BCVA and CST from baseline to month 12, number of injections, rate of completed follow-up and withdrawal rate, protocol deviations, rate of a letter score decrease of 15 or more letters from baseline, rate of rescue therapy, rate of cataract surgery, complications, and safety data reporting. Analysis was performed both on the entire cohort and based on the stratification.

Enrollment took place 4 weeks after the third loading injection for eligible patients, referred to as trial week 0. Recruited patients received a fourth intravitreal injection at this time and an additional mandated injection at trial week 4. Therefore, by trial week 4, all participants had received 3 loading injections and 2 trial injections. The trial week 4 injection was to be administered after vitrectomy for the vitrectomy group. From trial week 8 onward, participants were treated on a T&E basis.

Participants whose BCVA was within 5 letters and whose CST was within 50 µm for 3 consecutive trial visits had their intertreatment interval extended by 4 weeks. Worsening of VA by more than 5 letters or CST by more than 50 µm prompted reduction in the intertreatment interval by 4 weeks. Intertreatment intervals were not increased from 8 to 12 weeks at the 40- or 42-week visit to try to minimize CST and VA changes from treatment extensions coinciding with final visit measurements.

Figure 1. CONSORT Flow Diagram to Outline Recruitment Process



CST indicates central subfield thickness; DME, diabetic macular edema; VEGF, vascular endothelial growth factor.

From week 24 onward, participants with VA deterioration of 6 or more letters on 2 consecutive visits compared with trial baseline and attributable to increased CST were eligible for rescue treatment. Investigators had a choice of continuing 4 weekly injections, switching to an alternative anti-VEGF agent, or switching to intravitreal corticosteroid therapy as permitted by National Institute for Health and Care Excellence guidance.[16-18] Macular laser was not a permitted trial rescue therapy.

Patients were randomized by enrolling clinicians using a variable block randomization algorithm on a 1:1 basis to the vitrectomy or control group, stratifying for VMIA. VMIA was defined as vitreomacular traction or ERM involving the central macula. Vitreomacular adhesion was not classified as VMIA.[19]

Ophthalmologists and participants were not masked to the performance of vitrectomy, as a sham operation was judged unfeasible. To facilitate masking, outcome assessors were permitted access to the case report form but not to medical records where surgical procedures were recorded.

Baseline and final refracted BCVAs were measured as a single-letter scoring number of ETDRS letters using the COMPlog acuity measurement system.[20]

There was no a priori requirement for a study of a specific sample size to satisfy a power calculation. However, the aim based on available funding was to recruit 100 patients randomized 1:1 into vitrectomy plus standard care or standard care alone, further stratified into 2 equal groups, with and without VMIA, to provide information on the ability to recruit to a trial of this nature and to inform the power calculations of an RCT.

Statistical Analysis

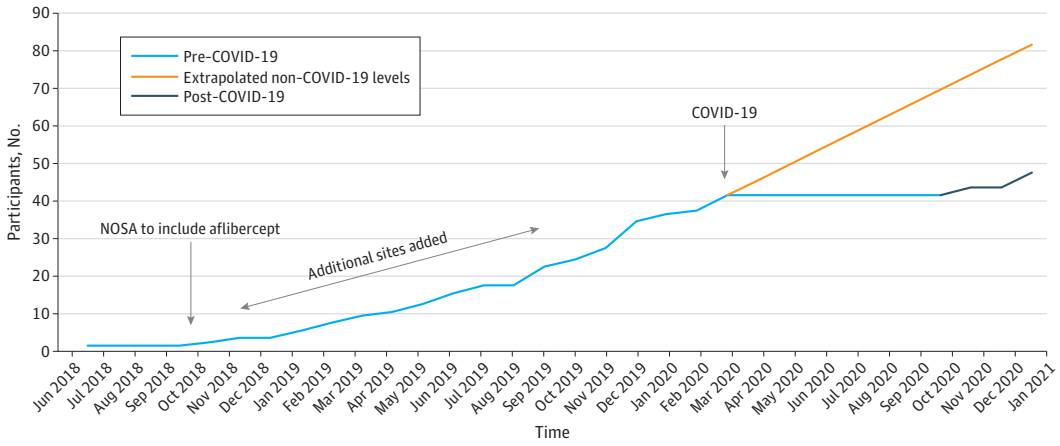
Results were analyzed with Stata statistical software release 16.0 for Mac (StataCorp LLC). Descriptive statistics were used to calculate demographic data. Means with SDs and medians with ranges or IQRs were presented where relevant. The Mann-Whitney *U* test was used to assess nonparametric continuous data, and the χ^2 test was used for categorical data. Where appropriate, comparative tests were performed using the paired *t* test or Wilcoxon rank sum test. All *P* values were 2-sided, and there was no adjustment for multiple analyses.

Results

Recruitment commenced at the first site in June 2018 and closed at all sites in January 2021, with 21 sites by December 2019. A total of 47 patients were recruited, including 23 patients (mean [SD] age, 66 [10] years) in the control group and 24 patients (mean [SD] age, 62 [12] years) in the vitrectomy group. Twenty participants in the control group and 22 in the vitrectomy group completed 12-month follow-up. Three patients (6%; 2 who had been randomized to vitrectomy and 1 to control) withdrew from the trial citing safety concerns regarding regular outpatient attendance during the COVID-19 pandemic. One patient was lost to follow-up, and 1 died of an unrelated health condition 4 months after recruitment (both had been randomized to the control group). No one in the vitrectomy group refused to undergo surgery. Outcome data from 42 participants (89%; mean [SD] age, 63 [11] years; 26 [62%] male) were analyzed. Rate of recruitment and association of the COVID-19 pandemic with recruitment are outlined in **Figure 2**. Baseline characteristics are displayed in **Table 1** and appeared comparable between trial groups.

No difference in 12-month BCVA was noted between groups, with a 12-month median (IQR) BCVA letter score of 73 (65-77) letters (Snellen equivalent, 20/40) in the control group vs 77 (67-81) letters (Snellen equivalent, 20/32) in the vitrectomy group (difference, 4 letters; 95% CI, −8 to 2; *P* = .24). There was no difference in BCVA change from baseline (median [IQR], −1 [−3 to 2] letters for the control group vs −2 [−8 to 2] letters for the vitrectomy group; difference, 1 letter; 95% CI, −5 to 7; *P* = .85). No difference was found in CST changes

Figure 2. Recruitment Numbers for the Vitrectomy in Diabetic Macular Oedema (VIDEO) Trial by Month From June 2018 Until January 2021



The inclusion of aflibercept, additional sites, and the first UK national lockdown due to COVID-19 are highlighted. NOSA indicates notification of substantial amendment.

Table 1. Baseline Demographic Characteristics for the Entire Cohort by Randomization Group

Characteristic	Control (n = 23)	Vitrectomy (n = 24)
Age, mean (SD), y	66 (10)	62 (12)
Type 2 diabetes, No. (%)	21 (91)	21 (88)
Diabetes duration, median (IQR), mo	180 (72-216)	192 (120-240)
HbA_{1c}, median (IQR), % of total hemoglobin	8.4 (7-11)	8.9 (7-9)
Baseline BP, mean (SD), mm Hg		
Systolic	144 (19)	136 (20)
Diastolic	80 (8)	74 (12)
Stratified to VMIA subgroup, No. (%)	6 (30)	6 (27)
Ethnicity[a]		
Afro-Caribbean	0	2 (8)
Asian subcontinental or Middle Eastern	4 (17)	4 (17)
White	18 (78)	18 (75)
Other	1 (4)	0
Baseline BCVA, median (IQR), ETDRS letters	75 (67-77)	77 (70-83)
Baseline CST, median (IQR), µm	397 (366-450)	396 (360-425)

Abbreviations: BCVA, best-corrected visual acuity; BP, blood pressure; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; HbA_{1c}, hemoglobin A_{1c}; VMIA, vitreomacular interface abnormality.

SI conversion factor: To convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01.

[a] Ethnicity data were self-reported and obtained at enrollment. Other was provided as an option for those who did not feel they could be categorized into the groups listed.

(median [IQR], −94 [−122 to 9] µm for the control group vs −32 [−48 to 25] µm for the vitrectomy group; difference, 62 µm; 95% CI, −110 to 11; P = .11).

Six patients (26%) in the control group and 6 patients (25%) in the vitrectomy group were stratified for VMIA. No cases of VMIA resolution were reported in the control group at 12 months, and VMIA was not present in any vitrectomy group participants at the trial end point. **Table 2** presents overall trial results, and the eTable in Supplement 2 shows results stratified for the presence or absence of VMIA.

Nine (21%) of the 42 patients who completed 12-month follow-up were pseudophakic at baseline, including 6 (14%) randomized to the control group and 3 (7%) to the vitrectomy group. A total of 5, all in the vitrectomy group (12% of the 42 patients overall, or 23% of the 22 patients in the vitrectomy group), underwent cataract surgery during the trial. No cataract surgery complications were recorded. The overall rate of cataract formation, including documented lens opacity and cataract surgery, was 25% in the control group and 46% in the vitrectomy group (P = .20).

Two severe but trial treatment-unrelated adverse events were reported, both within the control group. One patient died 4 months after recruitment while overseas. No cause-of-death information was available. One participant underwent hospitalization for a relapse of preexisting inflammatory bowel disease.

One participant in the vitrectomy group underwent cryotherapy for retinal breaks at the time of surgery. There were no other reported surgical complications or safety concerns identified, including no cases of retinal detachment or endophthalmitis.

Three (7%) of the 42 patients who completed 12-month follow-up had received rescue therapy. One participant from the vitrectomy group received 2 intravitreal sustained-release dexamethasone implant injections; the 12-month BCVA in that individual was 85 letters (Snellen equivalent, 20/20). One participant in the control group was switched from ranibizumab

Table 2. Secondary Outcomes

Characteristic	Median (IQR)		Difference (95% CI)	*P* value
	Control (n = 20)	Vitrectomy (n = 22)		
BCVA, ETDRS letters				
Baseline	76 (72 to 77)	78 (70 to 83)	2 (−9 to 2)	.14
Final	73 (65 to 77)	77 (67 to 81)	4 (−8 to 2)	.24
Calculated change	−1 (−3 to 2)	−2 (−8 to 2)	1 (−5 to 7)	.85
>15-Letter score loss, No. (%)	4 (20)	1 (5)	NA	.10[a]
CST, µm				
Baseline	408 (368 to 455)	398 (360 to 425)	10 (−16 to 44)	.37
Final	327 (301 to 414)	377 (317 to 420)	50 (−76 to 29)	.38
Calculated change	−94 (−122 to 9)	−32 (−48 to 25)	62 (−110 to 11)	.11
Injections, No.	8 (7 to 11)	9 (8 to 11)	1 (−2 to 0)	.09

Abbreviations: BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; NA, not applicable.

[a] Calculated using χ^2 test.

to aflibercept injections from week 24 and continued to receive monthly injections; the final BCVA in that individual was 60 letters (Snellen equivalent, 20/63). One other control participant received an intravitreal sustained-release dexamethasone implant injection at week 24 and no further injections; the final BCVA was 52 letters (Snellen equivalent, 20/100).

Discussion

The trial recruitment figures are displayed in Figure 2. Despite the intervening COVID-19 pandemic, which cancelled recruitment for more than a year, such a trial might be feasible regarding willingness of centers and patients to participate. We estimate that the COVID-19 pandemic halved the potential recruitment from participating centers within our available resources.

It can be seen from Table 1 that the trial groups appeared comparable at baseline and typical of those being managed for DME.[21] Comparing the last 2 rows of Table 1 and the first 2 data rows of Table 2 suggests that the loss of 5 participants did not likely substantially bias the results.

Overall, no differences in either 12-month BCVA (our primary functional outcome measure) or change in BCVA from baseline between the control and vitrectomy groups were identified. Similarly, no differences in median 12-month CST or change in CST between the vitrectomy and control groups (Table 2) were detected.

We also found no overall differences in the number of injections administered over the trial period between the 2 groups. The trial design mandated that all patients receive a minimum of 7 and a maximum of 12 injections. While data from Diabetic Retinopathy Clinical Research Network Protocol T have shown better visual outcomes in study participants treated with aflibercept compared with ranibizumab at 12 months when baseline visual acuity was 20/50 or worse,[22] aflibercept and ranibizumab treatments were evenly distributed across the 2 groups in our trial. We do not anticipate this observation to have had a substantial bias on the outcomes observed.

Historical data have suggested a beneficial effect of vitrectomy for DME when there is macular traction in the form of vitreomacular traction or ERM.[1,23] This trial therefore was stratified on the basis of the presence or absence of VMIA to explore such differential effects. The results presented in the eTable in Supplement 2 should be interpreted with caution due to the small numbers within these groups.

In participants with baseline VMIA, there were no differences in 12-month BCVA or in the secondary measures of CST, change in CST, and change in BCVA between the vitrectomy and control groups. A median of 9 injections were given in each group. However, with only 6 participants in each group, it is difficult to draw any relevant conclusions. In this RCT, however, no evidence of benefit of vitrectomy plus standard care over standard-care T&E anti-VEGF therapy alone in patients with DME and VMIA was suggested.

The eTable in Supplement 2 shows that in the absence of VMIA on optical coherence tomography, no differences in the primary outcome measure of BCVA at 12 months were noted. The effect of vitrectomy on CST may have been inferior to injections alone (CST reduction of 105 µm in the control group vs 6 µm in the intervention group; difference, 99 µm; 95% CI, −139 to −5; *P* = .04). Participants without VMIA who underwent vitrectomy also required a median of 10 injections compared with 8 in the control group. However, not all of the trial secondary outcome measures suggested an adverse effect of vitrectomy in the no-VMIA vitrectomy group: 3 participants in the control group had a 15-letter reduction in BCVA compared with only 1 participant in the vitrectomy group, and the median changes in VA were similar at −2 letters and −1 letter in the control and intervention groups, respectively. This result of an adverse effect of vitrectomy is biologically plausible and has been observed in other contexts. Vitrectomy may reduce the half-life of anti-VEGF therapy in the vitreous cavity,[24] although the Diabetic Retinopathy Clinical Research Network Protocol I suggested no relevance of prior vitrectomy on VA outcomes or injection number.[25] Regardless, this trial found no incremental benefit of vitrectomy over anti-VEGF therapy alone in the absence of VMIA.

The overall rate of cataract formation in this trial was 37% (25% in the control group and 46% in the vitrectomy group). This is in keeping with other studies on vitrectomy and supports the role of vitrectomy in cataractogenesis.[26] Presence of visually relevant cataract at the final visit appeared equally distributed, with 5 participants in each group, as were the

overall rates of pseudophakia at the trial end point (6 vs 8 patients in the control and vitrectomy groups, respectively).

A role for the vitreous in the formation of DME, by various mechanisms, has been postulated. The diabetic vitreous is abnormal, with enzyme-mediated vitreous collagen cross-linking and nonenzymatic glycation. This may result in reduced permeability or impaired diffusion[27] and/or act as a reservoir for inflammatory mediators.[28] The vitreomacular interface also has been implicated in the treatment response to DME. Mechanical etiologies ranging from a taut thickened hyaloid[29] to partial vitreomacular separation and/or ERM[1] have been suggested. The development of VMIA has been shown to worsen DME, while evolution of a PVD has been associated with improved VA and macular thickness.[30-35] A relatively large analysis on vitrectomy for DME by Jackson et al[26] has identified the capacity for anatomic improvements in eyes with DME. Jackson and colleagues reported variability in inclusion criteria, follow-up times, and outcome measures and cited a lack of high-quality evidence on the topic; they also identified the need for an RCT to assess the role of vitrectomy compared with anti-VEGF treatment.

In the absence of good data on the effectiveness of vitrectomy for DME and given that only 25% of patients with DME might be expected to respond suboptimally to anti-VEGF therapy, it was considered that a trial of vitrectomy alone vs standard-care anti-VEGF therapy in treatment-naive individuals might not offer equipoise.

Dugel et al[36] reported the long-term anatomic and visual gains in patients with less than 20% CST reduction from baseline to 12 weeks in a post hoc analysis of the Diabetic Retinopathy Clinical Research Network Protocol I study data.[37] Response to ranibizumab, in terms of CST reduction and VA response, at 12 weeks was found to predict anatomic and visual outcomes at 52 and 156 weeks.[38] Dugel and colleagues concluded that, despite intensive therapy and monitoring, for patients with limited CST reduction at 12 weeks, the likelihood of further improvement at 1 year was moderate at best. Therefore, the CST response at week 12 was considered a significant prognostic indicator for 1- and 3-year anatomic outcomes. Early response as a prediction of long-term response was also identified by Bressler et al,[39] who, in a previous analysis of the Protocol I data,[37] reported that an early and maintained anatomic response to ranibizumab was associated with better visual outcomes at 12 months when compared with patients with a slow response or no response.[39]

Limitations

There were limitations to the trial. Although details of the surgical processes were outlined in the protocol, surgical technique differs between surgeons and is difficult to standardize. Enrollment to the trial was reduced, and given the biological variability in outcomes, it is possible the sample sizes were not large enough to reject the null hypothesis. We applied a T&E regimen in this trial, but most large DME trials have used fixed dosing or dosing as needed.[5,21,40] However, given the growing use of T&E injections in the management of DME,[41] this may increase the generalizability of our findings.

The VIDEO trial was a randomized pilot trial to investigate the clinical effectiveness of vitrectomy and ILM peeling as an adjunct to T&E anti-VEGF therapy in patients who had suboptimally responded to prior anti-VEGF therapy and to assess the feasibility of running a definitive trial of this question.[36,38] These data are therefore not applicable to other scenarios, such as vitrectomy with or without ILM peeling as sole therapy, which has been reported to be successful in uncontrolled studies.[6,8]

Conclusions

Our results demonstrate that a full trial comparing standard care vs standard care plus pars plana vitrectomy may be feasible, although enrollment goals were not attained in this study. However, there was no evidence found to suggest a beneficial clinical effect of vitrectomy and ILM peeling as an adjunct to T&E anti-VEGF therapy alone.

ARTICLE INFORMATION

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Author Contributions: Dr Maguire had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Maguire, Laidlaw, Steel.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Maguire, Laidlaw, Almeida.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Maguire.
Obtained funding: Maguire, Laidlaw.
Administrative, technical, or material support: Maguire, Laidlaw, Muqit, Dinah, Hillier, Almeida, Hussain, Gordon-Bennet.
Supervision: Maguire, Laidlaw, Hammond, Steel, Lee, Almeida, Gordon-Bennet.

Conflict of Interest Disclosures: Dr Maguire reported receiving funding from Fight for Sight UK during the conduct of the study. Dr Laidlaw reported being an owner and developer of COMPlog Clinical Vision Measurement Systems Ltd outside the submitted work. Dr Steel reported receiving grants from Alcon, Dutch Ophthalmic Research Centre, BVI, Roche, Boehringer Ingelheim, Gyroscope, and Bayer and personal fees from Alcon, Alimera, Eyepoint, Dutch Ophthalmic Research Centre, BVI, Gyroscope, and Complement Therapeutics outside the submitted work. Dr Dinah reported receiving personal fees from Bayer and grants from Roche outside the submitted work.

Dr Hillier reported receiving personal fees from Roche outside the submitted work. Dr Jackson reported being a consultant or advisor to 2CTech, Alcon, Dutch Ophthalmic Research Centre, iLumen, Opthea, Outlook Therapeutics, Oxurion, and Regeneron and receiving conference support from Roche. The National Health Service receives site payments for patients recruited to commercial clinical trials, including trials of diabetic eye disease. No other disclosures were reported.

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