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RESEARCH ARTICLE

Photodynamic and Anti-VEGF Therapy for Polypoidal Choroidal Vasculopathy - 'Real World' Outcomes in a Caucasian Population

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Abstract:

Background:

The prevalence of polypoidal choroidal vasculopathy (PCV) is significantly higher amongst Asian populations compared to Caucasian, and evidence regarding the clinical outcomes of Caucasian patients is limited.

Objective:

This retrospective study sought to investigate real-world clinical outcomes of Caucasian PCV patients treated with polypoidal verteporfin photodynamic therapy (PDT) in combination with anti-VEGF therapy up to 36 months post-treatment.

Methods:

Consecutive PCV patients who received PDT between 2011 and 2017 were included. Mean change in visual acuity (VA) measured by ETDRS letter score and mean change in central subfield thickness (CST) were the main outcome measures. Data were collected at baseline, 3, 12, 24 and 36 months. Regression analyses were carried out on pre-treatment clinical features to determine if there were any factors associated with a good visual outcome (better than or equal to 70 ETDRS letters at 12 months).

Results:

Seventy six patients (96% Caucasian) and seventy eight eyes were included in the analysis. Mean change in VA was -1, -4, and 0 ETDRS letters at 12, 24, and 36 months, respectively. CST was reduced by a mean of -51, -54, and -55 microns at 12, 24, and 36 months, respectively. Better pre-treatment VA was the only pre-treatment clinical feature associated with a good visual outcome at 12 months (OR 1.16, p<0.001).

Conclusion:

PDT, in combination with anti-VEGF therapy, maintains VA and may reduce the anti-VEGF therapy burden in Caucasian patients with PCV. Better pre-treatment VA is associated with a good visual outcome.

Keywords: Anti-VEGF, Caucasian, Polypoidal choroidal vasculopathy, Photodynamic therapy, Real-world outcomes, Therapy.

Article History

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1. INTRODUCTION

Polypoidal choroidal vasculopathy (PCV), also termed aneurysmal type 1 neovascularisation [1], is characterized by polyp-like aneurysmal dilations arising from branching vascular networks (BVN) underlying the retinal pigment epithelium (RPE) [2 - 4]. Patients with PCV present with

recurrent serosanguinous maculopathy of varying severity from massive haemorrhage to small retinal pigment epithelial detachments (PEDs) with a small amount of subretinal fluid (SRF). Characteristic optical coherence tomography (OCT) features include steep sided PEDs, irregular shallow PEDs (the double layer sign) and pachychoroid vessels [5]. There is still controversy as to whether PCV is a sub-type of neovascular age-related macular degeneration (nAMD), or whether it is a separate clinical entity. There are several demographic, clinical and angiographic features that support its classification as a distinct diagnosis [6, 7]. PCV is not associated with typical

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AMD drusen, it is more prevalent amongst younger age groups and it is more prevalent amongst Asian and pigmented races [5, 8, 9]. Aneurysmal dilatations can be seen in the early phases of indocyanine green angiography (ICGA) in cases of PCV and this remains the gold standard for making the diagnosis [5].

The prevalence of PCV amongst Asian patients with presumed nAMD has been found to be as high as 22 – 54% [10, 11]. In Caucasian populations, this figure is smaller and studies have estimated prevalence between 4 – 22% [8, 11, 12]. Much of the literature investigating PCV outcomes stems from an Asian population base and less data exists assessing the outcomes of patients in Caucasian populations. Interestingly, a study of Caucasian nAMD patients who responded poorly to anti-VEGF treatment found the prevalence of PCV to be as high as 21.5% [13].

PCV can be treated with anti-vascular endothelial growth factor (VEGF) monotherapy, with anti-VEGF and verteporfin photodynamic therapy (PDT) in combination, or PDT monotherapy. In terms of polyp closure, PDT has been shown to be superior to anti-VEGF [14], however it is thought constriction of choroidal vessels after PDT leads to hypoxia in both the choroid and retinal pigment epithelium, which causes up-regulation of VEGF [15]. Therefore giving concurrent anti-VEGF helps protect against the sequelae of choroidal and RPE ischaemia as well as treat the exudative changes resulting from neovascularization [16].

Debate still remains as to which specific treatment regimen is the most effective [3]. Studies have demonstrated the effectiveness of anti-VEGF monotherapy with ranibizumab, aflibercept and bevacizumab as well as with PDT monotherapy [17 - 20]. However, combination therapy is thought to have the highest success rate with regard to both polyp closure and improved visual acuity (VA) [14, 21]. EVEREST II is the largest randomized controlled trial comparing combination therapy with anti-VEGF monotherapy [14]. This trial demonstrated that PDT, in combination with ranibizumab, improved VA by 8.3 ETDRS letters after one year, compared to an improvement of 5.1 letters in the ranibizumab monotherapy group.

Retrospective studies on ‘real world’ patients can provide valuable data on the effectiveness of treatments in routine clinical practice. We report results from a study of 76 patients (78 eyes) treated for PCV with PDT +/- anti-VEGF therapy and followed up to 36 months post baseline PDT, 96% of whom were Caucasian. This is one of the largest studies reporting PCV outcomes in a predominantly Caucasian population. The study investigates safety and efficacy outcomes for PDT in PCV, including a cohort of patients that received prior anti-VEGF treatment. In addition, we investigated whether there were any underlying clinical features which were associated with a good VA outcome.

2. METHODS

Consecutive patients who received PDT for a diagnosis of PCV in a tertiary referral centre between 2011 and 2017 were included in this retrospective study. The patients were either new referrals that were treatment naïve to both anti-VEGF and PDT or were refractory to anti-VEGF monotherapy for

presumed nAMD, and were referred for investigation for PCV with ICGA, and subsequent rescue PDT. Patients were identified as having PCV by a consultant ophthalmologist with a specialist interest in the medical retina based on clinical findings and imaging with ICGA and OCT. Standard practice in our centre is to carry out ICGA for the majority of patients with type 1 neovascularisation or with OCT signs suggestive of PCV.

Data were collected at baseline (clinic visit immediately prior to first PDT), and as close to 3, 12, 24 and 36 months intervals as possible. Data collected included age, sex, VA measured by ETDRS letter score, number of anti-VEGF treatments prior to first PDT, and number of retreatments with anti-VEGF and PDT. The majority of the VA measurements were recorded using ETDRS letter score, however a small number were recorded in Snellen VA. Snellen measurements were converted to ETDRS letter score using a recognized method [22] Central subfield thickness (CST) was recorded at each time point, measured from the central 1mm subfield using spectral domain OCT on the TOPCON 3D OCT-2000 (Topcon, Tokyo, Japan). In addition, baseline ICGA and fundal features were recorded, including the formation of polyps (single, cluster or string), location of polyps (foveal [within 500 microns of the foveal centre], extrafoveal or peripapillary), number of polyp areas (one or multiple), presence of any haemorrhage or exudate, and presence of massive haemorrhage (four disc areas or more).

This study included patients who had undergone long durations of treatment with anti-VEGF for presumed nAMD prior to treatment with rescue PDT. To investigate whether including this patient cohort had an effect on the outcomes of the patient population as a whole, a further analysis was undertaken to compare outcomes of patients receiving “early PDT” (those who had never received PDT or anti-VEGF prior to presentation) with “rescue PDT” patients (all patients with prior exposure to anti-VEGF).

All patients received PDT by infusion of verteporfin (6 mg/m²), followed 15 minutes later by administration of diode laser (690 nm) with 600 mW/cm² irradiance and duration of 83 s (50 mJ/cm² fluence) over the polyp and BVN area that was identified on ICGA [23]. Our standard management is to combine PDT with an initial course of three monthly anti-VEGF injections (ranibizumab or aflibercept). PDT monotherapy was planned for a minority of patients with less aggressive lesions, and lesions away from the foveal centre. In cases of persistent exudative changes, additional anti-VEGF was continued monthly on a PRN basis until exudative changes resolved. If the treating clinician suspected that the polyps were still open and active, repeat ICGA was carried out with subsequent further PDT if indicated. Polyp closure rate was not investigated because ICGA was only carried out if clinically indicated.

Univariate logistic regression was carried out on the above pre-treatment features to determine if there were any factors associated with a good or poor VA outcome at 12 months. For the purposes of this analysis, 70 letters or better was categorized as a good outcome (group 1), and worse than 70 letters was categorized as a poor outcome (group 2). A

Multivariate logistic regression model was then used to determine which predictors were independently associated with a good outcome. All analyses were done using Minitab (version 18) at a 5% significance level.

The research described adhered to the tenets of the Declaration of Helsinki, and as per local ethics guidance, no ethical approval was required for this study.

3. RESULTS

Baseline demographics immediately prior to PDT of the 76 patients are described in Table 1. The majority were female (68%) and of a Caucasian background (96%). The mean age at presentation was 73 years with a range of 18 – 87 years. With regard to the PCV lesion characteristics, 69% of eyes showed a cluster of polyps, and in 65% of cases, polyps were present in only one area. Polyps were located in the peripapillary and extrafoveal regions in approximately equal proportions at around 39%, with 18% of cases having polyps within 500 microns of the foveal centre. Haemorrhage was present in half of the patient cohort, with massive haemorrhage present in 5%. Two-thirds of patients were found to have macular exudation. From the 78 eyes recorded at baseline, data were available for 71, 59 and 41 eyes at 12, 24 and 36 months following PDT treatment, respectively. At 36 months follow up, there was a loss to follow up of 37 patients (39 eyes) as a result of patient death (n=5), transfer of care back to referring clinician (n=7), treatment success and subsequent discharge (n=8), treatment failure and subsequent discharge (n=11) and unknown loss to follow up (n=6).

Table 1. Baseline Demographics and Clinical Features (n=78).

Mean age at presentation (SD), years	73 (11)	-
Sex	Male	31.6%
	Female	68.4%
Ethnicity	Caucasian	96.1%
	Asian	1.3%
	African/Caribbean	1.3%
	Unknown	1.3%
Polyp location	Foveal	17.9%
	Extrafoveal	39.7%
	Peripapillary	38.4%
	Unknown	3.8%
Polyp formation	Cluster	69.2%
	String	12.8%
	Single	12.8%
	Unknown	5.1%
No. of polyp areas	One	65.4%
	Multiple	29.5%
	Unknown	5.1%
Macular exudate	Yes	66.7%
	Unknown	2.6%
Macular haemorrhage	Yes	50%
	Unknown	2.6%
Massive haemorrhage	Yes	5.2%
	Unknown	2.6%

Combination treatment with PDT and anti-VEGF was given to 89% of cases with the remaining patients receiving PDT only without any need for anti-VEGF therapy. Of those treated with anti-VEGF, 29% received initial treatment with ranibizumab and 70% received aflibercept. A small number of patients required repeat PDT (12 patients) and one patient received a third PDT treatment during the follow up period.

Of 78 eyes treated with PDT, 40 eyes received “rescue PDT” following prior treatment with anti-VEGF and 38 eyes were anti-VEGF naïve and received “early PDT”. Rescue PDT patients were seen in a clinic for a median of 1.72 years prior to receiving PDT and received an average of 4.96 injections in the 12 months prior to PDT, which reduced to an average of 2.60 injections in the 12 months following PDT, and 2.19 injections in the 12-24 month follow-up period. Early PDT patients received an average of 3.21 injections over the 12 months following PDT, but this included a standard loading dose of three anti-VEGF injections. A small number (n=7) of early PDT patients with peripapillary or lower risk extrafoveal lesions on ICGA were treated with monotherapy and had no exposure to anti-VEGF at 12 months follow-up. Analysis was performed to investigate any differences between early PDT and rescue PDT patients previously treated with anti-VEGF (Tables 2 and 3). Patients in the early PDT group had a mean loss of 5 ETDRS letters at 24 months and an improvement of 2 ETDRS letters at 36 months, with those in the rescue PDT group having a mean loss of 4 ETDRS letters at 24 and 36 months. The median VA pre-PDT and 12 months post PDT were significantly higher in the early PDT group. Due to the loss of follow-up, statistical analysis was not performed comparing rescue and early PDT outcomes beyond 12 months. To account for the 7 eyes lost to follow up by 12 months, an additional last outcome carried forward analysis was performed on the data in Table 3, and showed no significant differences.

Table 4 describes changes in VA and CST during the follow-up of the whole cohort. Patients maintained a stable VA with a mean of 56 letters observed at baseline and at three years follow up, respectively. CST was reduced by a mean of -51 microns at 12 months and this reduction was maintained for up to 36 months. A subgroup analysis comparing results by polyp location showed that patients with a peripapillary polyp location had a median improvement in VA from 63 to 70 ETDRS letters at 12 months. Those with an extrafoveal polyp location had no change in median VA at 12 months, and those with a foveal polyp location had a drop in median VA from 56 to 53 letters.

Table 5 displays univariate analyses carried out on pre-treatment factors to determine if there were any clinical features associated with a good visual outcome (VA ≥ 70 ETDRS letters) at 12 months post PDT. Of the 71 eyes included in this analysis, 21 (30%) had VA ≥ 70 ETDRS letters at baseline and 26 eyes had VA ≥ 70 ETDRS letters at 12 months. Better pre-treatment VA was associated with a good visual outcome with an odds ratio of 1.16 (p<0.001), indicating that for each additional one unit increase in pre-treatment VA, the odds of a good visual outcome increased by a factor of 1.16. The odds ratio for a favourable outcome with peripapillary lesions was 3.23 compared to foveal lesions, however this

finding did not reach statistical significance. There was also an association between haemorrhage at initial presentation with a poorer visual outcome (OR 0.40, p = 0.067), but this, again was not statistically significant.

There were two episodes of vision threatening complications immediately following PDT. They were both

retinal pigment epithelium tears and resulted in a reduction in VA of 22 letters and 3 letters at three months follow up, and 29 letters and 35 letters at 12 months follow up, respectively. One case of anti-VEGF related endophthalmitis was excluded from follow-up on the basis that it was not secondary to PDT. One patient suffered acute back pain at the time of the verteporfin infusion.

Table 2. Visual acuity and central retinal thickness at 0 to 36 months follow up in Early PDT and Rescue PDT subgroups.

Time From Follow Up	Baseline	3 Months	12 Months	24 Months	36 Months
Early PDT subgroup	n=38	n=37	n=36	n=31	n=21
Median VA (range), letters	63 (24-81)	65 (4-87)	69 (5-85)	61 (0-88)	68 (30-85)
Mean VA (SD), letters	62 (16)	61 (19)	61 (23)	57 (26)	64 (16)
Mean VA change from baseline, letters	-	-1	-1	-5	+2
Rescue PDT subgroup	n=40	n=39	n=35	n=28	n=20
Median VA (range), letters	54	53 (10-83)	52 (0-84)	54 (0-85)	57 (0-81)
Mean VA (SD), letters	51 (19)	51 (20)	49 (24)	47 (28)	47 (30)
Mean VA change from baseline, letters	-	0	-2	-4	-4

Table 3. Comparison of patients receiving early PDT vs. rescue PDT at 12 months.

	Early PDT (n=36) Median (IQR)	Rescue PDT(n=35) Median (IQR)	95% CI	p-value
Age	78 (66, 82)	74 (67, 81)	-2.6, 6.5	0.433
ETDRS Letter Score pre-PDT	63 (52, 73)	54 (36, 85)	3.0, 19.0	0.008
CST pre-PDT	277 (222, 327)	288 (232, 355)	-53.0, 26.0	0.532
ETDRS Letter Score 12 months post-PDT	69 (51, 79)	52 (35, 73)	3.0, 25.0	0.022
CST 12 months post-PDT	227 (205, 268)	216 (190, 285)	-28.0, 29.0	0.778

Table 4. Visual acuity and central retinal thickness at 0 to 36 months follow up in all patients.

Time From Follow Up (n)	Baseline (78)	3 Months (76)	12 Months (71)	24 Months (59)	36 Months (41)
Median VA (range), letters	60 (0-85)	60 (4-87)	59 (0-90)	60 (0-89)	60 (0-85)
Mean VA (SD), letters	56 (18)	56 (20)	55 (24)	52 (27)	56 (25)
Mean VA change from baseline, letters	-	0	-1	-4	0
Median CST (range), microns	279 (118-604)	218 (145-597)	223 (117-665)	222 (132-413)	222 (121-494)
Mean CST (SD), microns	295 (103)	227 (69)	244 (90)	241 (97)	240 (82)
Mean CST change from baseline, microns	-	-68	-51	-54	-55

Table 5. Univariate analyses to determine which pre-treatment factors were associated with a good visual outcome (VA ≥ 70 Letters) at 12 months post PDT.

Clinical Characteristic	Variable 1	Variable 2	Odds Ratio	Confidence Interval	P Value
Age	-	-	0.97	(0.93, 1.01)	0.140
Sex	Male	Female	0.55	(0.18, 1.66)	0.281
ETDRS Letter Score pre-PDT	-	-	1.16	(1.08, 1.24)	<0.001
CST pre-PDT	-	-	1.00	(0.99, 1.00)	0.921
Total no. of Anti-VEGF pre-PDT	-	-	0.93	(0.84, 1.02)	0.106
Presence of Haemorrhage	Yes	No	0.40	(0.15, 1.08)	0.067
Presence of Exudate	Yes	No	1.28	(0.43, 3.76)	0.652
No. of Polyp areas	Single	Multiple	2.10	(0.62, 6.37)	0.180
Location of Polyp	Foveal	Extrafoveal	0.63	(0.14, 2.88)	0.211
-	Peripapillary	Extrafoveal	2.05	(0.70, 5.97)	-
-	Peripapillary	Foveal	3.23	(0.71, 14.61)	-

(Table 5) contd.....

Formation of Polyp	Single	Cluster	0.37	(0.07, 1.95)	0.459
-	String	Cluster	0.86	(0.21, 3.43)	-
-	String	Single	2.33	(0.31, 17.54)	-

4. DISCUSSION

This is one of the largest retrospective studies of PCV patients within a Caucasian population. The inclusion of all patients, regardless of prior treatment or comorbidity, reflects a real world population and increases our understanding of what realistic outcomes are for PCV patients treated with a combination of PDT and anti-VEGF therapy. However, the authors acknowledge that this methodology may also be deemed a weakness as the study population was varied and included both early PDT and rescue PDT patients previously treated with anti-VEGF therapy. In addition to the recognized limitations of a retrospective, non-randomized study, there were three different consultants managing the patients included in the study, which introduces the possibility of variations in practice even with best efforts to standardize treatment regimens.

PDT is more effective at inducing polyp closure when compared to anti-VEGF monotherapy [14], which may result in a reduced requirement for ongoing anti-VEGF injections with resulting benefits to patients and health service providers. Patients previously treated with anti-VEGF were assessed on their need for further anti-VEGF following initial treatment with PDT in this study. We showed that patients who had previously received multiple anti-VEGF injections as monotherapy had a reduced requirement for anti-VEGF during the 24 months following rescue PDT.

Due to the lack of availability of ICGA facilities in many of the referring hospitals, many previously treated patients in our cohort were initially not known to have underlying PCV disease and were treated as nAMD with anti-VEGF monotherapy. A proportion of PCV patients will respond to anti-VEGF monotherapy, so these patients were not referred for consideration for PDT and, therefore, not included in this study. If patients did not respond as expected to anti-VEGF in their local hospital, they were referred to our centre for further investigation with ICGA and treatment with rescue PDT. Therefore this group of PCV patients were a more difficult to treat group with resistance to anti-VEGF monotherapy, and this may have contributed to poorer visual outcomes in our cohort when compared to the existing literature. We found that rescue PDT patients had a significantly poorer VA when compared to early PDT patients prior to PDT treatment. From the regression analysis, we observed that patients starting with poorer vision were more likely to have a poorer outcome following PDT, however we did observe that in the rescue PDT cohort, anti-VEGF was a burden that was lessened following treatment with PDT. ICGA remains the gold standard for diagnosing PCV and its lack of availability can lead to a delay in diagnosis and optimal treatment. A study of 202 nAMD patients with sub-optimal response to anti-VEGF by Hatz *et al.* [13] found a high prevalence of PCV (21.5%) and that without ICGA facilities, the diagnosis of PCV can be easily missed, resulting in a delay for optimal treatment. There needs to be greater awareness and appropriate investigation of PCV in Caucasian

populations, and early referral to centres with ICGA and PDT services is likely to lead to improved clinical outcomes.

Data describing clinical outcomes in Caucasian populations receiving treatment for PCV is limited. Agorogiannis *et al.* found a stable VA in 48 eyes treated with combination therapy, PDT monotherapy or anti-VEGF monotherapy in a 12-month retrospective study [6]. Davis *et al.* found a mean increase in 2.5 letters in a retrospective review of 27 patients treated with combination therapy and followed up for a mean of 15.8 months [24 - 26]. On the other hand, there is a large body of evidence investigating the outcomes of PCV patients in primarily Asian populations. The landmark prospective RCTs EVEREST II and PLANET found better visual outcomes than were observed in our study. EVEREST II described an increase of 8.3 ETDRS letters at 12 months follow up for combination therapy with ranibizumab [14, 24]. The PLANET study showed an increase of 10.7 letters at 12 months follow up for treatment with aflibercept and rescue PDT, however only 13% of patients had rescue PDT in this trial [24]. Retrospective studies of Asian PCV populations also support favourable visual outcomes at 12 months and beyond with combination treatment. A large meta-analysis by Wang *et al.* investigating outcomes pooled from 543 eyes in two RCTs and nine retrospective studies showed improved mean VA up to 24 months post combination treatment in patients predominately of Asian origin [25]. On average, our collective patient group had either the same or less than five letters loss at each time point up to 36 months. When the early PDT group was looked at separately, there was an average loss of five letters of vision up to 24 months follow-up, then a mean gain of two letters at 36 months. The rescue PDT group recorded a mean loss of four letters at 24 and 36 months, and the median VA was significantly lower pre and post treatment when compared to the early PDT group. A retrospective real world study by Ratanasukon *et al.* of Asian PCV patients treated with rescue PDT following initial anti-VEGF found an overall mean loss of 0.95 letters after four years follow-up [10]. Our data suggest that Caucasian PCV patients have poorer outcomes when previously treated with anti-VEGF therapy. In addition, our results for early PDT patients were worse than published controlled trials and real world retrospective studies, suggesting that Caucasian PCV patients do not respond as well to combination treatment when compared to Asian patients. However, more data is needed to corroborate this hypothesis.

The literature published assessing PCV outcomes amongst Caucasian populations is limited, however from the evidence that is known, and the findings in this study, it appears that visual outcomes are less favourable when compared to Asian populations. This may be due to treatment centres in countries with a predominately Caucasian population underdiagnosing PCV, which then leads to a delay in referral to a tertiary centre for appropriate management. There needs to be greater awareness of PCV as the possible underlying diagnosis in Caucasian patients with neovascular maculopathy. In addition, further research is needed to inform clinicians what the optimal

management plan should be for this group of patients.

CONCLUSION

PDT, in combination with anti-VEGF therapy, maintains VA and may reduce the anti-VEGF therapy burden in Caucasian patients with PCV. Better pre-treatment VA is associated with a good visual outcome. Visual outcomes of Caucasian PCV patients treated with PDT in combination with anti-VEGF therapy are less favourable when compared to Asian populations.

LIST OF ABBREVIATIONS

PCV	= Polypoidal choroidal vasculopathy
PDT	= Photodynamic therapy
nAMD	= Neovascular age related macular degeneration
CRT	= Central retinal thickness
ICGA	= Indocyanine green angiography
VA	= Visual Acuity
ETDRS	= Early treatment diabetic retinopathy study
SRF	= Subretinal fluid
BVN	= Branching vascular network
OCT	= Optical coherence tomography
Anti- VEGF	= V Vascular endothelial growth factor
PED	= Pigment epithelial detachment

AUTHORS CONTRIBUTION:

KMG: Designed, collected and analysed data. Principal author in drafting and revising the manuscript.

DY: Interpretation of data and statistical analysis

AJ: Conception and acquisition of data and revision of the manuscript

MP: Conception and acquisition of data

DFG: Conception, analysis and interpretation of data, substantive manuscript revision and editing

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

As per national guidelines, no ethical approval was required for this study. Affirming this, the recommendation of the West of Scotland Research Ethics Service was that no ethical approval or written consent from participants was required for this study.

(NHS Health Research authority – “Governance arrangements for research ethics committees: 2020 edition)

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. All the humans were used in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (<http://ethics.iit.edu/ecodes/node/3931>).

CONSENT FOR PUBLICATION

Affirming this, the recommendation of the West of Scotland Research Ethics Service was that no ethical approval or written consent from participants was required for this study.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data was compiled from electronic patient records and is held securely by the hospital trust. Copies of the data are available upon request.

FUNDING

None.

CONFLICT OF INTEREST

D.F.G. has been supported to attend educational meetings by Novartis (November 2017) and Bayer (January 2019). A.J. has been supported to attend an educational course by Bayer. Other authors have no competing interests.

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