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Multi-Spot Lasers: What Constitutes an Effective Pan Retinal Photocoagulation (PRP) and is it Time to Find a New Treatment Regime?

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ABSTRACT

Purpose: To assess the effectiveness of the multispot (PASCAL) Pan Retinal Photocoagulation (PRP) laser in treating Proliferative Diabetic Retinopathy (PDR) as there are concerns that patients may be undertreated with multi-spot lasers resulting in worsening disease. Additionally to correlate various risk factors with progression of disease.

Methods: We performed a retrospective study of 56 patients (80 eyes) with PDR treated with a multi-spot PASCAL laser at a single hospital site. Diabetic control, ethnicity and area of treated retina (calculated using the radius of the burn and magnification factor of the lens utilized) was correlated with PDR progression over 1 year and compared with ETDRS guidelines of an area treated ≥236mm2 to control progression.

Results: At 12 months, 65% eyes had progression of PDR. This included development of pre-retinal haemorrhage (4%), vitreous haemorrhage (23%) and requirement for vitrectomy surgery (10%). The mean burn area in this group was 310mm2 compared to 536mm^2 in eyes that did not progress (p= 0.0091). Asian and Black African/ Caribbean patients appear to be at increased risk of severe progression compared to white ethnic groups but HbA1c correlation was less conclusive. High risk PDR was also a risk factor for severe progression.

Conclusion: To reduce the risk of progression of PDR, if using a multi-spot laser, it is recommended to treat an area between 236mm^2 (approx. 1900 burns of 400 mm burns at the retina) and 536mm^2(approx. 4,250 burns of 400 mm burns at the retina). More aggressive treatment is likely to be required in Asian and African/Carribean patients, in those with high risk PDR and where patients have suddenly dropped their HbA1c. To reduce the impact on visual field, it is likely that a combination of anti-VEGF and laser is needed. PRP laser however is likely to continue to be an important, long-term effective treatment for PDR.

INTRODUCTION

Diabetic retinopathy causes significant morbidity through retinal ischaemia, neovascularistion and haemorrhage causing reduced visual acuity and blindness. Correctly identifying and effectively treating sight-threatening retinopathy reduces visual loss in this high-risk patient group [1]. Research performed by the Diabetic Retinopathy Study (DRS) research group, [2] published more than 40 years ago now, have shown that treatment of Proliferative Diabetic Retinopathy (PDR) using Pan

Retinal Photocoagulation (PRP) significantly reduced the risk of visual loss. Since the publication of Protocol S [3] and Clarity studies [4],which compared PRP laser treatment to anti-VEGF monotherapy and showed that Anti-VEGF treatment with Ranibizmab [3] and Aflibercept [4] were both non-inferior to PRP laser in treating PDR, many may feel that PRP treatment is no longer required. Anti-VEGF agents however have their limitations, predominantly due to cost, treatment burden and lack of long-term effect. PRP laser treatment therefore remains the mainstay of treatment in those with PDR.

Traditionally the argon green laser has been used to perform PRP. Current guidelines on how to perform PRP published by both the American Academy of Ophthalmology and the Royal College of Ophthalmologists are based on evidence provided by the DRS and the Early Treatment Diabetic Retinopathy Study (ETDRS) in which the argon green laser was used to perform treatment [5,6]. ETDRS guidelines recommended that when performing PRP laser, a spot size of 500µm should be used at the retina with a duration of 100ms with a minimum area of 236mm^2 to be treated [7]. Over the years, the development of the pattern scan laser (PASCAL) has resulted in a movement away from the use of the argon green laser when performing PRP. PASCAL uses a shorter pulse duration of 20ms compared to 100ms and administers multiple burns on one depression of the foot pedal. PASCAL has been shown to reduce the time taken to treat the retina and to reduce pain experienced by the patient making it a more acceptable treatment for patients when compared to the traditional argon green laser [8,9].

There is, however, a concern that patients may be undertreated with PASCAL if using current treatment guidelines developed for use with the argon laser. Increased recurrence of neovascularisation has been seen after treatment of PDR with PASCAL compared to argon laser despite equivalent spot numbers being administered [10]. Some studies have reported comparable outcomes although PASCAL machines required a higher power during treatment and follow up in the studies was minimal, ranging from 2.5 to 5.9 months [11-13]. It has been recognized that due to the smaller spot size, a greater number of spots are needed for the equivalent area to be treated. In the Manchester PASCAL study, they showed that 3 patients with severe PDR, needed 6924 PRP laser burns which made up an area of 836 mm^2 [14]. This is 3.5 times the area recommended by ETDRS [7].

Our audit aimed to look at outcomes at 1 year in patients with PDR treated with the PASCAL laser in a teaching hospital setting and to correlate the area of retina treated with progression of their disease. As this was considered to be a retrospective service evaluation of routine practice, Ethical Committee Approval by the Trust was not required.

METHODS

A retrospective audit of cases of PDR treated with PRP using a PASCAL at a single hospital site was performed. Patients were identified using an electronic database of all laser patients and diabetic retinal screening referrals over the course of a year. Data were collated regarding age, sex of patient, ethnicity, most recent HbA1c reading (mmol/mol), number of PRP sessions performed, PASCAL settings used (including spot diameter and number of spots administered) and lens type used for treatment. Evidence of PDR progression over 12months post initiation of PRP was recorded from the electronic patient record and hospital notes. Evidence of progression was graded as: 0= no progression, 1= greater than 3 laser sessions required to control proliferation, or further PRP required more than 3 months post initial treatment; 2= further documented new vessels seen; 3= preretinal haemorrhage; 4= vitreous haemorrhage; 5= tractional retinal detachment or vitrectomy required. Patients were excluded if they had previously received PRP laser treatment to the retina with the exception of previous macular laser for treatment of clinically significant macula oedema. Patients were not included if the above data set was incomplete. If patients were seen at 6 months post treatment with no follow up at 12 months recorded they were still included in our results at 12 months using an intention to treat analysis. Three laser treatments or treatment within the initial 3 months were allowed to ensure that patients were given adequate PRP treatment in the first instance. Each sitting of laser treatment was typically between 600-1200 burns, 200microns spot size (dialed into the machine) with 250-350 mw power setting. Any further laser treatment given after 3 months was defined as being due to a failed PRP treatment.

The area of retina treated in each case was calculated using the PASCAL spot diameter and the type of lens used to calculate the spot size at the retina; this was 1.44x

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multiplication factor if the VOLK transequator lens had been used and 2x for the VOLK superquad lens. The spot size area was calculated using the spot radius (r) and the formula "circle area= πr^2". This was multiplied by spot number to calculate area of retina treated. An intention to treat analysis was used to calculate rates of progression at 12 month follow up; rate of progression was compared between groups with different areas of retina treated. The area of retina treated in our sample was compared to current ETDRS guidelines recommending a minimum of 236mm2 of retina that should be treated [7].

For statistical analysis, the Chi-squared test was used to calculate the significance of different progression rates at different recommended burn areas. The Mann-Whitney U test was used to calculate the significance of the different burn areas between groups who progressed and those that stabilized at 12 months.

RESULTS

Complete data sets were obtained for 56 patients with treatment naive eyes who received multispot treatment for PDR at a single teaching hospital site during the specified time period. The patients' ages included in the study ranged from 27-83 years. Twenty-six female and 30 male patients were included. The ethnicity of the patients is given in (Table 1). Twenty-five of the patients had both of their eyes treated for PDR, resulting in data for 81 eyes being collated. One eye was excluded as the total burn area was recorded as 28.7mm^2; suggestive of a partial sectoral PRP rather than a complete PRP. Eighty eyes of 56 patients were included in our final analysis. Nineteen out of eighty eyes were considered to have high-risk PDR with High Risk Characteristics [2], 46 low risk PDR and 15 unknown. The number of high risk PDR cases may be lower than expected but in the UK, PDR is picked up at an earlier stage due to the National Diabetic Eye Screening Programme [1]. Twenty-two eyes had focal or grid laser treatment either previous to or in the year following the PRP treatment for Clinically Significant Macular Oedema (CSME). Ten out of 80 eyes had one or more Anti-VEGF treatments during the course of the year following PRP treatment either pre-vitrectomy or a course of treatment for significant diabetic macular oedema. One eye had a dexamethasone implant (Ozurdex) inserted following the laser treatment. No OCT or fundus fluoresce in angiography data were collected during the study to assess macular thickness or extent of ischaemia. Analysis of data took place at 6 and 12post treatment. 73 of the 80 patient eyes had documented evidence of review at 12 months. 7 eyes were lost to follow up following initial review at 6 months; 6 of these had evidence of progression recorded at this point and 1 did not. All of these eyes were included in the data analysis.

Table 1: Ethnicity of patients.

Ethnicity	Total
White	26
Black African/Caribbean	23
Asian	7
Grand Total	56

Table 2: Area of retina treated and number of eyes with progression of retinopathy.

Area of retina treated (mm^2)	No of multi-spot laser equivalent burns (400µm at the retina)	Number of eyes with specified area treated	Number of eyes with progression over 12 months
≥236	1,878	38/80 (47.5%)	20/38 (52.6%)
≥536	4,265	21/80 (26.2%)	8/21 (38.1%)

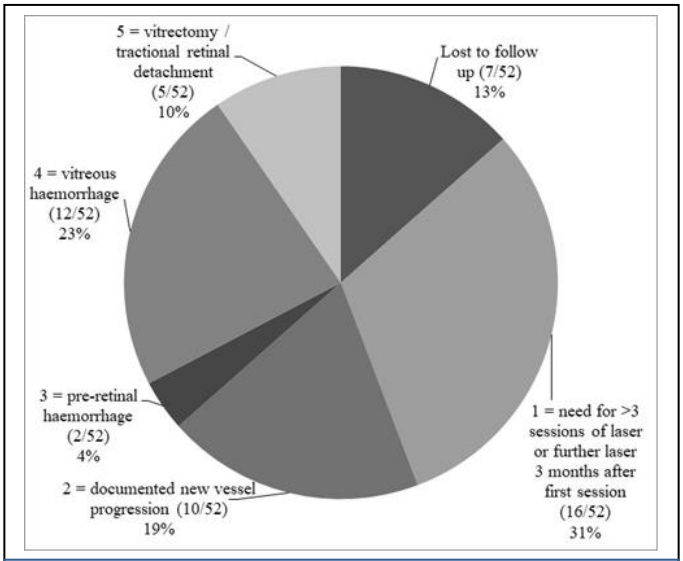

Figure 1: Grading of eyes with progression of diabetic retinopathy at 12 months (n=52/80).

PRP treatment was performed over 1 session in 21 cases,2 sessions in 55 cases and over3 sessions in 4 cases.

According to an intention to treat analysis, at 12 month review, there was evidence of progression in 52/80 (65%)patient eyes

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(Figure 1) with 23% progressing to vitreous haemorrhage and 10% requiring a vitrectomy within 1 year of treatment. There are several factors that may have contributed to this progression including diabetic control.

The most recent HbA1c from the hospital database was recorded at the time of the PRP laser treatment in 52/56 patients ranging from 32-112 mmol/mol (median 77 mmol/mol: Normal Range 20-42 mmol/mol). The progression of retinopathy by HbA1c value is given in (Figure 2). This shows a weak or slightly negative correlation (r^2= -0.0137) whereby a higher HbA1c number does not give rise to an increased risk of progression of retinopathy over 1 year follow up. The burn area was also correlated with HbA1c (Figure 3) which shows a weakly positive correlation (r^2 = 0.0063) implying that poorly controlled diabetes was weakly correlated with a higher burn area in terms of initial PRP treatment.

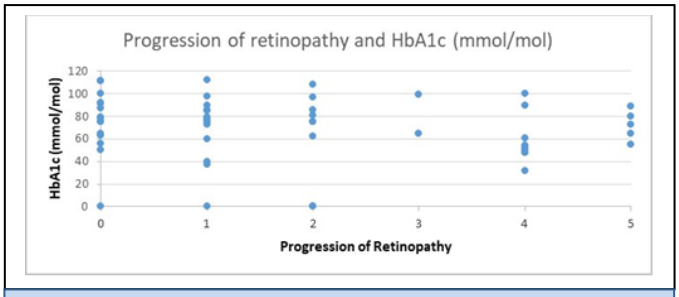

Figure 2: Progression of retinopathy by HbA1c (mmol/mol) (r^2= -0.0137).

0: no progression
1: need for further laser
2: documented NV increase
3: pre-retinal haemorrhage
4: Vitreous Haemorrhage
5: Vitrectomy or TRD (traction detachment)

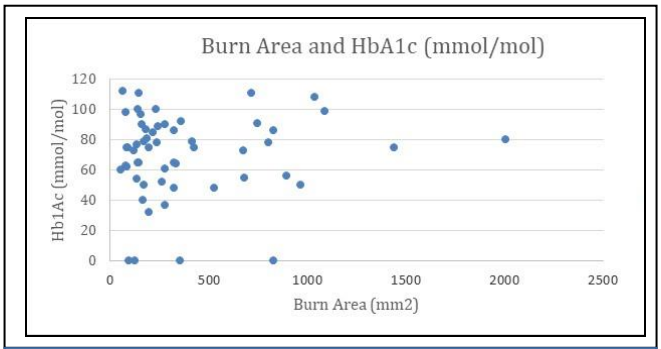

Figure 3: Burn area correlated with HbA1c (r^2 = 0.0063).

In terms of the laser treatment itself, the mean area of treated retina in eyes that had progressed at 12 months was significantly less than those which had not progressed: 310mm^2 compared to 536mm^2 respectively (p=0.0091, Mann-Whitney-U test). 44/59 (74.6%) of eyes with a retinal burn area <536mm^2 progressed at 12 months compared to only 8/21 (38.1%) of those with a retinal burn area of equal or greater than 536mm2(p=0.0026, Chi-squared test)- (Table 2). A burn area of 536 mm^2 would equate to approximately 4,265 burns at 200µ (set at the machine) using a superquad lens creating a burn of 400µ on the retina. At 12 months there was also a significant difference in rate of progression in eyes with an area of retina treated greater or equal to that recommended by ETDRS (236mm2) (p= 0.027, Chi-squared test) see (Table 2) and (Figure 4,5).

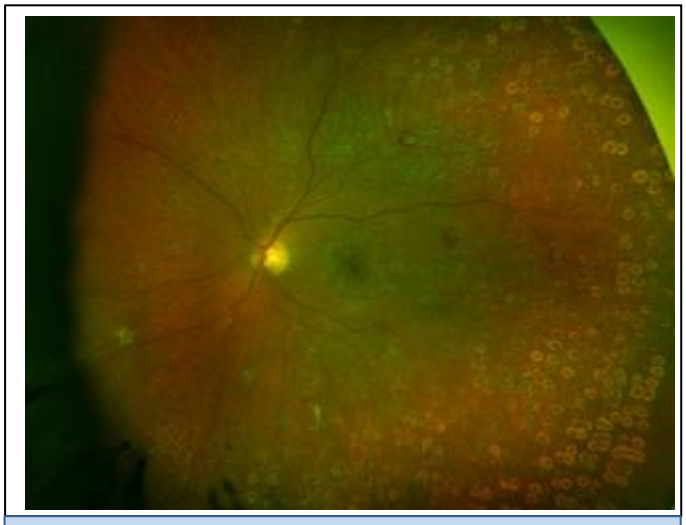

Figure 4: An Optos image example of a patient with greater than 236mm^2 burn area (338mm^2) with no progression at 1 year.

In terms of ethnicity (Figure 4) it appears that Black Afro-Caribbean and Asianpatientsalthough not statistically significant have a higher risk of progressing to severe disease (vitreous haemorrhage or Vitrectomy/Traction Detachment)compared to White ethnic groups (Figure 6) although the numbers are small to be able to make any definite conclusions.

DISCUSSION

This study looks at possible factors (including retinal ablation area) relating to progression of diabetic retinopathy post PRP laser in a group of 56 patients with PDR treated with pan-

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retinal photocoagulation using a PASCAL multispot laser at a single hospital site. Diabetes duration and diabetic control are known to affect retinopathy progression [5,6]. Unfortunately, one of the limitations of this study was the inability to assess diabetes duration but HbA1c (mmol/mol) was available to assess control. The median (77 mmol/mol: Normal Range 20-42) was high indicating the relative poor control of the study group. Interestingly there was low correlation between the HbA1c level and Progression levels of retinopathy (Figure 2) but this may because high HbA1c can take more than a year to impact on retinopathy levels. Additionally 2 of the patients had had previously very high HbA1c levels (>100 mmol/mol) prior to the study which had normalized around the time of PRP treatment (they were therefore recorded to have low HbA1c in the study). These 2 patients both progressed to a vitrectomy and high level of progression.

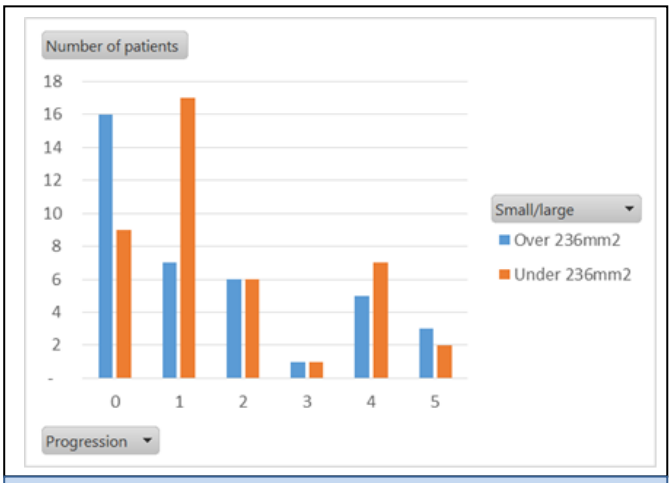

Figure 5: Retinopathy progression levels in those with treated area <236 mm^2 and ≥236mm^2.

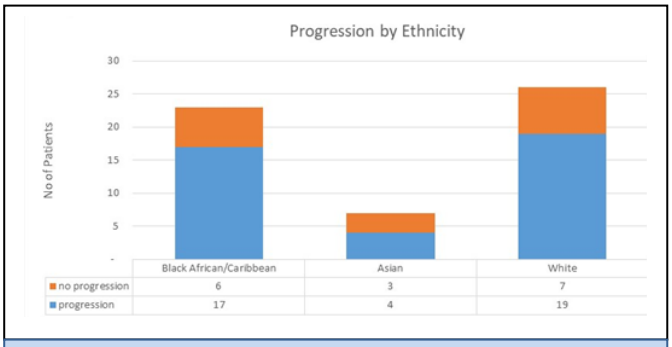

Figure 6: Progression of Retinopathy (worse eye) (n=56) by Ethnicity.

	Black African/ Caribbean	Asian/ Indian/ Bangladeshi	White/ White Other
no progression	6 (26%)	3 (43%)	7 (27%)
progression	17 (74%)	4 (57%)	19 (73%)
severe progression (4,5)	7 (30%)	3 (43%)	5 (19%)

Ethnicity is thought to affect diabetic retinopathy levels. From this study it appears that the Black Afro-Caribbean and Asian ethnic groups had a higher proportion of eyes (30% and 43%) that progressed to severe retinopathy (vitreous haemorrhage or vitrectomy or TRD) compared to White ethnic groups (19%) (Figure 6). Possible explanations may include genetic factors or possible higher hypertension levels in these groups.

Other factors relating to progression of retinopathy include the laser treatment parameters. It is known that regression of neovascularisation is related to the area of retina treated with laser [15]. ETDRS and DRS guidelines recommend a minimum burn area of 236mm^2, which equates to 1200 burns using the traditional argon laser with a 500µm spot size at the retina. When performing PRP with PASCAL using a 200µm spot size (with a Superquad lens with a magnification factor of x2) you would need approximately 1,878 burns to treat the same area of retina. If these factors are not considered then the treatment may be sub-therapeutic. This may explain why many of the eyes reviewed progressed over the follow up period as just over half the eyes (52.5%) were treated with a smaller area of ablation.

(Figure 5) shows that these eyes with less than 236mm^2 of treatment were more likely to need further laser treatment and had a greater risk of vitreous haemorrhage over the subsequent year. Those eyes that progressed to Vitrectomy or TRD had a greater retinal area treated. This is most likely explained by the fact that these were the eyes with High Risk Characteristics (HRC) at baseline. They would have been likely to be treated more aggressively in the first instance. It is also interesting that when HbA1c is correlated to burn area (Figure 3), there is a slight positive correlation. Again those with worse diabetic control, were more likely to have documented further progression of new vessels and further PRP applied. (Figure 4) shows an example of a patient with greater than 236mm^2 burn area with no progression at 1 year and an HbA1c 50 mmol/mol.

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Although we were not able to ascertain all patients with high risk characteristics of PDR (HRC-PDR) at baseline, we know that 19 were identified in this group. Of these, 6 went on to have vitreous haemorrhages and five had Vitrectomies for either persistent vitreous haemorrhage or tractional detachment. As expected, this forms a high risk group for progression but is not the only factor involved. Forty-six patients had low risk characteristics at baseline and 15 were unknown. In the UK, due to most referrals coming from the National Diabetic Eye Screening Programme, proliferative diabetic retinopathy is able to be picked up in the early stages and referred on for treatment.

It is also important to consider other factors such aslaser pulse duration [16] and type of lens used (and associated magnification factor) which also influence the final retinal burn area. Salman demonstrated that a higher power was additionally required when using the PASCAL for the treatment of PDR since the duration of the burn was less (20-30ms) compared to 100ms using the traditional Argon laser [12].

An increased failure rate with the PASCAL laser has also been shown in other studies. Chappelow et al [10] and the Manchester Pascal Study [14] showed the need to increase treatment with PASCAL laser compared to traditional argon laser with areas up to 836mm^2 required to achieve regression of severe PDR.

The main concern with a high number of burns and large retinal ablation areas would be the impact on the peripheral visual field and loss of night vision. Mathematical modelling of the retina by Davies suggested that by reducing burn spacing and extending treatment to the or a serrata upwards of 1600 burns with a 500 µm spot size may be placed to allow adequate treatment whilst conserving the driving field required by the UK DVLA[17].

An interesting finding from the 5 year Protocol S study [3], showed that even though the group receiving ranibizumab for PDR experienced significantly less peripheral visual field sensitivity loss at 2 years, by 5 years the ranibizumab group had increasing levels of visual field loss [18]. This implies that other factors are at play apart from PRP laser related Visual Field loss. This may be related to increasing peripheral ischaemia or due to the reduction in Anti-VEGF treatments in subsequent years. of the study.

In our study, although 22 eyes had focal/grid laser treatment for clinically significant macular oedema, only 10 eyes had anti-VEGF injections following laser and 1 eye had a dexamethasone implant. These numbers may be considered lower than expected. This may be due to 2 reasons. Firstly in the UK, we are restricted to using anti-VEGF agents in only those eyes where the central macular thickness is greater than 400 microns (NICE guidance 2013) and dexamethasone implants (Ozurdex) can only be used in pseudophakic eyes. Secondly, it is likely that those eyes treated with anti-VEGF agents are less likely to develop PDR and therefore not likely to be ascertained as part of this study. There are of course benefits of treating PDR with Anti-VEGF agents instead of PRP laser alone including reduced diabetic macular oedema (DMO) rates [3], reduced vitrectomy rates [3,4] and reduced progression of retinopathy features [19].

The disadvantages include the significant cost burden(particularly the licensed anti-VEGFs such as ranibizumab and aflibercept) and the burden of regular clinic appointments over many years for injections with a short treatment effect. Additionally, there is the potential risk of endophthalmitis [3] and the risk of poorer outcomes with tractional retinal detachment and neovascularization of the iris in those that are lost to follow up seen in Protocol S [20]. Looking at alternative treatment regimes, a study looked at Optos guided, targeted PRP for PDR which showed that 76% regressed at 12 weeks following treatment but 30% still required further laser treatment over the subsequent year [21]. This suggests that targeted PRP treatment does not work and that PRP treatment should be considered as a fixed dose (of at least 236mm^2) rather than a variable amount of laser required.

In response to our initial question, of what constitutes an effective PRP? We would encourage the treatment of an area of retina, if using a multi-spot laser, of between 236mm^2 (approx. 1900 burns of200 mm using a superquad lens) and 536mm^2 (approx. 4,250 burns of 200 mm using a superquad lens),with much of the treatment being performed over at least 2 sessions. If eyes have high-risk characteristics, the higher retinal ablation area is recommended as these cases are more likely to do badly and may result in a Tractional Retinal Detachment or Vitrectomy.

Our study also suggests that more laser treatment is likely to be required in Afro Carribean or Asian patients who may be at greater risk of progression compared to other ethnic groups. Regarding HbA1c,this was a less conclusive risk factor. In those however, with a recent large drop in HbA1c, we would advocate more aggressive treatment as they may be at particular risk of progression to severe disease. To limit the impact on visual field, future research must focus on finding the ideal combination of laser treatment with anti-VEGF injections to find the optimum number and size of PRP multi-spot burns to give the best long-term outcome. Any new treatment regime has to balance the treatment burden of injections, avoiding significant visual field loss, preventing progression/ recurrence of PDR and reducing the risk of worsening when lost to follow up. Only then will we have a truly effective treatment for this potentially blinding condition.

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