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Abstract

Purpose: To determine factors affecting the visual outcome in eyes with retinal vasculitis and the rate of neovascularisation relapse in ischemic vasculitis.

Design: Retrospective cohort study

Methods: We reviewed 1169 uveitis patients from Moorfields Eye Hospital, UK. Retinal vasculitis was observed in 236 eyes (121 ischemic, 115 non- ischemic) that were compared to a control group (1022 eyes) with no retinal vasculitis. Ultra-widefield fluorescein angiography images were obtained in 63 eyes with ischemic vasculitis to quantify area of nonperfusion measured as ischemic index.

Results: The risk of vision loss was significantly more in retinal vasculitis compared to the non-vasculitis group (HR 1.67, C.I. 1.24 - 2.25, p=0.001). Retinal vasculitis had twice the risk of macular edema compared to non-vasculitis group. Macular ischemia increased the risk of vision loss in vasculitis eyes by 4.4 times. The use of systemic prednisolone in eyes with vasculitis was associated with a reduced risk of vision loss (HR 0.36, C.I 0.15-0.82, p=0.01). Laser photocoagulation was administered in 75 eyes (62.0%), out of which 29 (38.1%) had new vessels relapse and required additional laser treatment. The median ischemic index was 25.8% (IQR 10.2 – 46%). Ischemia involving ≥ 2 quadrants was associated with increased risk of new vessels formation (HR 2.7, C.I. 1.3-5.5, p=0.003).

Conclusions: Retinal vasculitis is associated with an increased risk of vision loss, mainly secondary to macular ischemia, and has a higher risk of macular edema compared to eyes with no vasculitis. Ischemia involving ≥ 2 quadrants is a risk factor for new vessels formation.

24th of February, 2017

Dear Professor Parrish,

Thank you for your email dated 23rd of February 2017 and for the useful comments regarding our manuscript **AJO-16-1631R1** titled "***Clinical outcome of retinal vasculitis and predictors for prognosis of ischemic retinal vasculitis***". We have addressed the issues as follows:

1. The AJO uses AMA reference style, which currently requires journal issue numbers. Please go to www.ajo.com and see the information for authors. The first and last page of every article are required and the issue number should appear in parentheses.

Response: The issue numbers has been added to each referenced article. The first and last page numbers for reference articles are all present.

2. Please remove the line numbering from your manuscript file; our system adds them automatically.

Response: This has been removed now in the manuscript

3. Submitted design: Design: Retrospective study. Suggested design: Retrospective cohort study

Response: The design now has been changed to (Retrospective cohort study) both in the abstract and method sections.

We hope this revised manuscript meets your requirements for publication.

Yours sincerely,

Oren Tomkins-Netzer.

Title page

Clinical outcome of retinal vasculitis and predictors for prognosis of ischemic retinal vasculitis.

Abbreviated title:

Ischemic retinal vasculitis clinical outcome

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Introduction:

Retinal vasculitis is a clinical finding in 6-15% of eyes with uveitis.[1,2] It can present most commonly as an idiopathic condition, and sometimes in association with an underlying infectious or systemic disease such as Behçet's disease, sarcoidosis, multiple sclerosis, collagen-vascular diseases,[3,4] or as an isolated ocular disease such as in sympathetic ophthalmia. Retinal vasculitis presents clinically as a spectrum, varying from mild venous sheathing to severe obstructive vasculitis. Vascular damage can result in loss of vessel wall integrity, leakage of blood constitutes into the retinal extracellular space and development of cystoid macular edema (CME), a significant factor contributing to vision loss.[5] Areas of retinal non-perfusion can result in irreversible vision loss, especially when results in macular ischemia [6] and can induce neovascularization (NV), with its consequences such as recurrent vitreous hemorrhage, traction retinal detachment, rubeosis iridis, and neovascular glaucoma which can also lead to permanent vision loss.[5] Retinal NV may occur in retinal vasculitis associated with severe intraocular inflammation even in the absence of retinal ischemia.[7]

Treatment of retinal vasculitis depends on the underlying cause, extent of vessel involvement, effect on visual acuity and presence of retinal complications, such as retinal ischemia and NV. Treatment of inflammation includes the use of corticosteroids while adding other immunomodulatory therapy if needed as a steroid sparing agent or to provide additional therapy to control the inflammation. Laser photocoagulation is the mainstay in managing NV. However, the role of retinal laser and anti-inflammatory medications in preventing further NV formation and ischemia progression has not been addressed.

The aim of this study is to assess the clinical outcome and risk factors related to vision loss in retinal vasculitis, as well as the rate of progression of retinal ischemia and NV formation after initial management with retinal laser photocoagulation.

Materials and Method:

This retrospective cohort study included adult patients who attended the uveitis clinic of a single consultant (S.L.) at Moorfields Eye Hospital in United Kingdom between February 2013 and May 2016. The study received institutional review board approval (ethical approval for data collection: ROAD16039, visual loss in uveitis; Clinical Trials registry no., NCT01983488). Eyes with intermediate, posterior and panuveitis were included and divided into two groups based on the presence or absence of retinal vasculitis. Patients were considered to have retinal vasculitis according to the Standardization of Uveitis Nomenclature Working Group (SUN) criteria, which considered perivascular sheathing and vascular leakage or occlusion on fundus fluorescein angiography (FFA) as evidence of retinal vascular disease.[8] Patient case notes were reviewed for any documentation of perivascular sheathing or exudates or intraretinal haemorrhage and had FFA showing vascular fluorescein leakage or occlusion which supports the diagnosis of vasculitis.[2] Patients with retinal vasculitis were further sub-divided into ischemic retinal vasculitis (IRV) and non-ischemic retinal vasculitis (non-IRV). Retinal ischemia was defined as an area of hypofluorescence on FFA of at least one disc diameter representing retinal non-perfusion or capillary dropout.[9] Exclusion criteria for eyes with ischemic vasculitis included missing or poor quality FFA images, the presence of concomitant diabetes

mellitus, sickle cell disease, ocular tumour/vasoproliferative lesion, or the presence of extensive areas of chorioretinal scarring prior to the diagnosis of retinal ischemia.

Best corrected visual acuity (BCVA) measured using snellen chart was collected from baseline and annually up to the final visit. Baseline was defined as the time of the first visit with a diagnosis of uveitis or, for the IRV group, time of diagnosis of retinal ischemia. BCVA results were converted to logarithm of the minimum angle of resolution (LogMAR) for analysis purposes. Vision loss was defined as BCVA ≤6/15 according to the SUN working group criteria.[8] In eyes with IRV, the incidence of NV formation treated with retinal laser photocoagulation and the rate of NV relapse requiring further laser therapy was documented.

FFA images were either taken using a digital retinal camera system (Topcon TRC 50IX; Topcon Medical Systems Inc, Paramus, NJ) or the ultra-wide field imaging (Optos PLC, Dunfermline, Scotland). For the purpose of quantifying the area of retinal nonperfusion, only eyes with ultra-widefield FFA were included to calculate the ischemic index using previously described methodology[10–12]. In this method, the total area of capillary nonperfusion seen in arteriovenous phase image was measured and expressed as a percentage of the total image area in pixels. This was done by one co-author using the manual area measurement function in ImageJ software (ImageJ 1.44p, National Institutes of Health, Bethesda, MD, USA). The central FFA images were used to measure the total image area for calculating the ischemic index, thus avoiding areas of peripheral distortion of the wide-field image owing to the spherical curvature of the eye. However, peripherally steered FFA images were used to determine the extent and boundaries of the peripheral nonperfusion. The Definition of new vessels at the optic nerve disc (NVD), new vessels elsewhere (NVE), and new vessels on iris (NVI) was based on FFA findings. Other FFA findings that were documented included the presence of macular ischemia, and angiographic CME. Macular ischemia was defined as a foveal avascular zone (FAZ) ≥ 1,000 µm at its widest diameter, or broken perifoveal capillary rings at the borders of the FAZ.[13] Angiographic CME was defined as macular leakage present at 5-10 minutes post fluorescein sodium injection.

Statistical analysis:

Categorical variables were presented as frequencies of distribution while continuous variables were reported as mean and standard error (SE) except when lack of normality in distribution was observed for which case it was reported as median and interquartile range (IQR). Mann-Whitney test was used to compare continuous variables between two groups while Chi-square test was reserved for categorical variables. Repeated measurement analysis was performed using Generalized Estimating Equation to compare mean difference (MD) in BCVA over follow-up period from baseline and between groups, aiming to eliminate possible correlation effect between the two eyes of the same patient. The hazard ratio (HR) and 95% confidence interval (C.I) for vision loss and uveitis complications were measured using Cox proportional hazards regression analysis. Analyses were performed with the SPSS statistical software (version 21, IBM, USA). A p-value of < 0.05 was considered to be statistically significant.

Results:

In this study, 1169 case records of patients with uveitis were reviewed, among which retinal vasculitis was observed in 163 patients (14%). After applying the exclusion criteria, we compared the outcome of 142 patients (236 eyes) with retinal vasculitis to 584 patients (1022 eyes) with intermediate, posterior or panuveitis but no vasculitis. There was no significant difference in the average follow-up time between the two groups [7.9 (0.58) years versus 7.8 (0.20) years, p=0.80]. The mean age at diagnosis was 42.5 (0.5) years in non vasculitis group and 40 (1.13) years for the vasculitis group (p=0.18). Male gender were slightly more predominant in the vasculitis group compare to the non-vasculitis one [80 patients (56.3%) versus 261 patients (44.0%), p=0.014).

Visual and clinical outcome of retinal vasculitis versus non-vasculitis

The BCVA at time of diagnosis of uveitis showed no significant difference between the vasculitis group compared with non-vasculitis one, both with a median of 0.18 LogMAR and IQR of 0.00 to 0.48 LogMAR (p= 0.52). In eyes with retinal vasculitis, the mean change in BCVA from first measure at baseline did not show a significant difference at one year (-0.08, SE0.03, p=0.05), five years (-0.07, SE 0.04, p=0.06) and ten years (-0.10, SE 0.05, p=0.05) follow-up period. The risk of vision loss was significantly greater in eyes with retinal vasculitis compared to those with no vasculitis (HR 1.67, 95% C.I. 1.24 - 2.25, p=0.001), with the risk persisting even after adjusting for the presence of CME (HR 1.44, 95% C.I 1.06-1.96, p=0.018), but lost significance when adjusted for the presence of macular ischemia (HR 1.33, 95% C.I 0.95-1.85, p=0.08]. Risk factors contributing to vision loss among both non-vasculitis and vasculitis groups are listed in Table 1. In eyes with retinal vasculitis, macular ischemia remained a significant factor that increased the risk of vision loss by more than four times even after adjusting for other associated complications (HR 4.4, 95% C.I 2.0-9.6, p<0.001). Eyes with retinal vasculitis had more than twice the risk of developing CME compared to non-vasculitis group (HR 2.2, 95% C.I 1.6-2.5, p=<0.001).
Systemic prednisolone was used in the management of 168 eyes (71.2%) with vasculitis compared to 640 eyes (63.0%) without vasculitis with no significant difference between the two groups (HR 1.06, 95% C.I 0.8-1.2, p=0.49). Immunosupressants were used in the management of 69 eyes (29.2%) with retinal vasculitis compared to 144 eyes (14.2%) with no vasculitis. Eyes with retinal vasculitis were twice as likely to require 2nd line immunosupressants when compared to non-vasculitis eyes (HR 2.0, 95% C.I 1.5-2.7, p=<0.001).

Ischemic retinal vasculitis compared to non-ischemic vasculitis

Among the 142 patients (236 eyes) with retinal vasculitis, 65 patients (115 eyes) had non-IRV, while 77 patients (121 eyes) had IRV. There were no major differences in baseline characteristics between the two groups apart from the mean follow-up time which was longer for the non-IRV group (7.7 versus 4.4 years, p=<0.001) (Table 2).

Changes in BCVA from baseline in eyes IRV were statistically significant over one year (-0.13, SE 0.03, p<0.001), five years (-0.14, SE 0.04, p=0.001) and ten years (-0.16, SE 0.04, p=0.001) follow-up period, unlike eyes with non-IRV in which changes in BCVA overtime were not significantly different from baseline. Vision loss occurred in 29 (23.0%) eyes with IRV and 29 (25.2%) of eyes with non-IRV. Over time the risk of vision loss was slightly more significant in eyes with IRV versus non-

IRV (HR 1.84, 95% C.I.1.07- 3.17, p=0.027). When looking at the two most common aetiological groups, there was no significant difference in the risk of vision loss between IRV and non-IRV among patients with idiopathic vasculitis (HR 1.04, p= 0.93) as well as patients with Behcets disease (HR 2.2, p= 0.34). The median time for the onset of vision loss in eyes with ischemia was 0.2 years (IQR 0 to 2.7 years) compared to non-IRV which had a median onset of vision loss of 1 year (IQR 0 to 5.5 years). The risk of developing CME was significantly greater among eyes with IRV compared to non-IRV group (HR 2.0, C.I 1.3-3.1, p<0.001).

The risk factors contributing to vision loss in eyes with IRV and non-IRV are presented in Table 3. CME in eyes with IRV was 2.5 times more likely to cause vision loss after adjusting for the presence of macular ischemia and use of systemic prednisolone (HR 2.5, 95% C.I 1.8-5.7, p=0.03). Macular ischemia was observed in 19 eyes (15.7%) with IRV, all of which were diagnosed at the initial presentation with ischemic vasculitis with no incidence during the follow-up period. Macular ischemia increased the risk of visual loss by 9.2 times (p<0.001). The use of systemic corticosteroids had a protective effect in preventing visual loss even after adjusting for the presence of macular ischemia and CME (HR 0.33, 95% C.I 0.14 – 0.77, p=0.01).

Characteristics of the retinal ischemia among the studied group

Retinal ischemia was already established during first visit with uveitis in 70 eyes (57.8%). In the remaining 51 eyes, ischemia occurred at a median of 7 years (IQR 2.0 – 9.3 years) following the diagnosis of uveitis. The area of ischemia was localised to the peripheral area in 45 eyes (37.2%), extended to the midperipheral area in 45 eyes (37.2%), and involved the posterior pole in 31 eyes (25.6%). The area of retinal ischemia was measured in 63 eyes with ultra-widefield FFA. The median ischemic index was 25.8% (IQR 10.2 – 46%).

Established complications of retinal ischemia included vitreous hemorrhage in 26 eyes (21.5%), NVD in 18 (14.9%), NVE in 75 (62.0%), and NVI in 4 eyes (3.3%). Retinal laser photocoagulation was administered in 75 eyes (62.0%), out of which 29 eyes (38.1%) had NV relapse and required an additional laser treatment (14 for treating NV at a new location and 15 for NV that failed to respond to the initial laser therapy). The first retinal laser photocoagulation was given at a median of 5 months (IQR 1-12) from baseline, ranging from 0 to 179 months post diagnosis of ischemia. The additional laser given for NV relapse was given at a median of 10.5 months (IQR 7.75 – 23.5) from the initial laser, ranging from 5 to 76 months. The time between uveitis diagnosis and first laser treatment was not significantly different in eyes with NV relapse post first laser versus those with no NV relapse (Median 5.0 months for both groups, p=0.31 Mann-Whitney test). Ischemia involving ≥2 quadrants was associated with an increased risk of NV formation (HR 2.7, C.I. 1.3-5.5, p=0.003) but was not significantly associated with risk of NV relapse (Table 4).

Discussion:

In this study, we examined the impact of retinal vasculitis on vision loss, as well as the progression of IRV. We found that (1) Vasculitis eyes were more likely to develop vision loss than eyes without vasculitis, mainly secondary to macular ischemia. (2) Eyes with retinal vasculitis had more than twice the risk of CME compared to non-vasculitis. (3) Eyes with IRV had greater risk of vision loss than eyes with non-IRV, mainly secondary to macular ischemia and CME. 4) Systemic corticosteroids were an important protective factor, reducing the risk of vision loss in both IRV and non-IRV eyes. (5) Retinal ischaemia involving two or more quadrants of the retina is significantly correlated with the initial NV formation.

Eyes with vasculitis had significantly worse visual outcome compared to the non-vasculitis eyes, and this was mainly related to the presence of macular ischemia in the vasculitis cases. A study examining 53 patients with idiopathic retinal vasculitis found severe vision loss to occur more often in eyes with ischemic vasculitis (34%) compared to the non-ischemic group (6%).[14] In our study cohort, macular ischemia and CME were related to vision loss, suggesting a direct involvement in ocular morbidity among eyes with vasculitis. This finding was consistent with the results observed in a recent study on 82 eyes with vasculitis in which poor visual acuity was independently associated with central macular thickness and the size of foveal avascular zone.[15] The increased risk of CME in the IRV compared to the non-IRV group in our study was also observed in a previous study [16] which suggests that additional factors apart from inflammation are involved in producing CME in eyes with IRV and that areas of nonperfusion may also promote the release of elevated levels of vascular endothelial growth factor (VEGF) leading to increased vascular permeability and development of CME, as seen in cases of diabetic retinopathy and retinal vein occlusion.[10] We should also consider the additional risk of panretinal photocoagulation itself in inducing CME and thus increasing its prevalence among eyes with IRV.[17]

Most of the eyes with retinal ischemia received their initial laser treatment within the first year following the diagnosis of ischemia, suggesting the need to closely observe ischemic retina during this period for the development of NV. Among eyes with IRV that underwent laser treatment, 38.1% required more than one session of laser photocoagulation. The rate of receiving additional laser therapy in our cohort was similar to that observed in a study on Eales' disease in which 47% of eyes that underwent laser therapy required additional retinal laser photocoagulation.[18] The need for additional laser therapy in our study did not reflect an increased risk of vision loss. The study found that retinal ischaemia involving ≥2 quadrants can significantly increase the risk of NV formation. This is similar to a study on IRVAN cases which suggested using laser photocoagulation in eyes with retinal ischaemia even before NV is formed when there is more than two quadrants affected with capillary non-perfusion.[20]

In our cohort, the use of corticosteroids was associated with a reduced risk of vision loss, including eyes with IRV and non-IRV. The use of corticosteroids and other anti-inflammatory medications in managing vasculitis and some of its associated complications, such as CME, contributes to their role in preventing vision loss[19]. Interestingly, macular ischemia developed early in the diagnosis of IRV, with no incidence observed over the rest of the follow up period; thus the role of

immunosuppressant medications in preventing macular ischemia should be addressed in future studies. However, we did not find a significant role for immunosuppressant medications in preventing ischemic relapse and NV formation.

The study has a number of limitations related to its retrospective nature and the selection of patients with heterogeneous underlying diseases. However, the common clinical presentation of retinal vasculitis and its functional consequences, suggest that the outcome of these conditions can be collated and examined together. Furthermore, retinal ischemia is an uncommon occurrence in conditions associated with retinal vasculitis and this paper represents a unique opportunity to examine the long-term visual outcome of eyes with ischemic vasculitis and the rate of progression of NV formation following laser therapy and immunosuppressive treatment. Another limitation was associated with the use of Optos FFA images in measuring the peripheral area of ischaemia. Due to the spherical curvature of the eye, ultra-widefield images commonly associated with blurred areas within the far periphery when the central portion of the image is in focus. When we excluded these blurred far peripheral areas, the total area measured is slightly smaller than the 200 degree achieved by the ellipsoidal mirror within the Optos imaging system.

In conclusion, the long term visual outcome in eyes with retinal vasculitis is worse when compared to eyes without vasculitis, mainly due to the risk of macular ischemia. The control of vasculitis with the use of systemic immunosuppressant and specifically systemic corticosteroids is an essential part in vasculitis management as it provides long-term protection by preventing further deterioration in visual function. It is also recommended to apply laser photocoagulation when ≥ 2 quadrants of retina are affected by capillary non-perfusion as this group carries a higher risk of NV formation.

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O.TN has board membership and received consultancy fees from AbbVie.

Reference

1. Paović J, Paović P, Vukosavljević M. Clinical and immunological features of retinal vasculitis in systemic diseases. *Vojnosanit Pregl Mil-Med Pharm Rev*. 2009;66 (12):961-965.
2. Rosenbaum JT, Ku J, Ali A, Choi D, Suhler EB. Patients with retinal vasculitis rarely suffer from systemic vasculitis. *Semin Arthritis Rheum*. 2012;41(6):859-865.
3. Walton RC, Ashmore ED. Retinal vasculitis. *Curr Opin Ophthalmol*. 2003;14 (6):413-419.
4. Bhaleeya SD, Davis J. Imaging retinal vascular changes in uveitis. *Int Ophthalmol Clin*. 2012;52 (4):83-96.
5. El-Asrar AMA, Herbort CP, Tabbara KF. A clinical approach to the diagnosis of retinal vasculitis. *Int Ophthalmol*. 2010;30(2):149-173.
6. Bentley CR, Stanford MR, Shilling JS, Sanders MD, Graham EM. Macular ischaemia in posterior uveitis. *Eye Lond Engl*. 1993;7(Pt 3):411-414.
7. Tugal-Tutkun I, Onal S, Altan-Yaycioglu R, Kir N, Urgancioglu M. Neovascularization of the optic disc in Behçet's disease. *Jpn J Ophthalmol*. 2006;50 (3):256-265.
8. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol*. 2005;140(3):509-516.
9. Wessel MM, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S. Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema. *Br J Ophthalmol*. 2012;96 (5):694-698.
10. Prasad PS, Oliver SCN, Coffee RE, Hubschman J-P, Schwartz SD. Ultra wide-field angiographic characteristics of branch retinal and hemicentral retinal vein occlusion. *Ophthalmology*. 2010;117(4): 780-784.
11. Tsui I, Kaines A, Havunjian MA, et al. Ischemic index and neovascularization in central retinal vein occlusion. *Retina Phila Pa*. 2011; 31(1):105-110.
12. Sim DA, Keane PA, Rajendram R, et al. Patterns of peripheral retinal and central macula ischemia in diabetic retinopathy as evaluated by ultra-widefield fluorescein angiography. *Am J Ophthalmol*. 2014;158(1):144-153.
13. Early Treatment Diabetic Retinopathy Study Research Group. Classification of diabetic retinopathy from fluorescein angiograms. ETDRS report number 11. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1991;98(5 Suppl):807-822.
14. Palmer HE, Stanford MR, Sanders MD, Graham EM. Visual outcome of patients with idiopathic ischaemic and non-ischaemic retinal vasculitis. *Eye Lond Engl*. 1996;10 (Pt 3):343-348.
15. Karampelas M, Sim DA, Chu C, et al. Quantitative Analysis of Peripheral Vasculitis, Ischemia, and Vascular Leakage in Uveitis Using Ultra-Widefield Fluorescein Angiography. *Am J Ophthalmol*. 2015; 159 (6):1161-1168.
16. Ali A, Ku JH, Suhler EB, Choi D, Rosenbaum JT. The course of retinal vasculitis. *Br J Ophthalmol*. 2014;98 (6):785-789.
17. McDonald HR, Schatz H. Macular edema following panretinal photocoagulation. *Retina Phila Pa*. 1985; 5(1): 5-10.

18. Dehghan MH, Ahmadieh H, Soheilian M, Azarmina M, Mashayekhi A, Naghibozakerin J. Therapeutic effects of laser photocoagulation and/or vitrectomy in Eales' disease. *Eur J Ophthalmol*. 2004;15 (3): 379-383.
19. Ermakova NA. Efficacy of corticosteroids and cyclosporin in the treatment of retinal vasculitis in patients with Behçet's disease. *Adv Exp Med Biol*. 2003; 528: 563-565.
20. Rouvas A, Nikita E, Markomichelakis N, Theodossiadis P, Pharmakakis N. Idiopathic retinal vasculitis, arteriolar macroaneurysms and neuroretinitis: clinical course and treatment. *J Ophthalmic Inflamm Infect*. 2013; 3 (1): 21.

Table 1

Table 1 Risk factors for vision loss in eyes with vasculitis compared to non-vasculitis

Factors	Non-Vasculitis				Vasculitis			
	Crude		Adjusted		Crude		Adjusted	
	HR (CI)	P value	HR (CI)	P value	HR (CI)	P value	HR (CI)	P value
Male gender	1.26 (0.9-1.6)	0.10	-	-	2.6 (0.9-7.5)	0.07	-	-
Age	1.02 (1.01-0.03)	**<0.001**	1.02 (1.01-1.03)	**<0.001**	1.05 (1.01-1.10)	**0.03**	1.06 (0.9-1.1)	0.06
Corneal opacity	1.33 (0.4- 4.1)	0.62	-	-	-	-	-	-
Cataract	1.2 (0.9-1.6)	0.21	-	-	1.1 (0.50-2.4)	0.38	-	-
Macular edema	1.39 (1.01-1.9)	**0.04**	1.17 (0.8-1.6)	0.38	1.42 (0.6 – 3.0)	0.36	-	-
Macular RPE Atrophy	1.66 (1.02-2.7)	**0.04**	1.06 (0.63-1.8)	0.82	1.4 (0.3 – 5.7)	0.64	-	-
Macular scar	3.1 (2.0-4.8)	**<0.001**	3.7 (2.3-6.0)	**<0.001**	2.0 (0.2-15.1)	0.47	-	-
Macular ischemia	-	**-**	-	-	7.7 (3.5-16.9)	**<0.001**	4.4 (2.0-9.6)	**<0.001**
ERM	1.44 (0.004-2.0)	**0.048**	1.04 (0.68-1.6)	0.82	0.5 (0.2-1.3)	0.20	-	-
Optic neuropathy	3.0 (1.8-4.9)	**<0.001**	3.4 (2.0-5.7)	**<0.001**	4.2 (1.7-10.0)	**0.001**	2.28 (0.8-6.2)	0.10
Retinal detachment	2.92 (1.7 – 4.8)	**<0.001**	3.6 (2.1-6.2)	**<0.001**	4.9 (1.5-15.9)	**0.008**	2.4 (0.7-8.3)	0.16
Use of systemic prednisolone	1.05 (0.77-1.42)	0.73	-	-	0.36 (0.15-0.82)	**0.01**	0.18 (0.05-0.6	**0.005**
Use of Immunomodulatory medications	1.73 (1.15-2.60)	**0.008**	1.53 (1.00-2.30)	0.05	1.10 (0.51-2.37)	0.80	-	-

ERM, Epiretinal Membrane; RPE, Retinal Pigmented Epithelium; CI, Confidence Interval; HR, Hazard ratio

Table 2 Demographic and clinical characteristics of 142 patients with retinal vasculitis

Variables	Ischemic vasculitis 77 patients, 121 eyes	Non Ischemic 65 patients, 115 eyes	P value*
Age, years; median (IQR)	37.7 (29 - 48)	40.5 (28 - 52)	0.82
Follow up, years; median (IQR)	4.4 (1.4 – 8.9)	7.7 (3.8 - 11.7)	<**0.001**
Male; n (%)	47 (61.0)	33 (55.8)	0.23
BCVA at baseline Median (IQR), LogMAR	0.18 (0.00-0.60)	0.18 (0.00-0.48)	0.28
BCVA at last follow up visit Median (IQR), LogMAR	0.18 (0.00-0.30)	0.18 (0.00-0.48)	0.52
Uveitis classification; n eyes (%)			
• IU	31 (25.6)	52 (45.2)	
• PU	38 (31.4)	10 (8.7)	-
• PANU	52 (43.0)	53 (46.1)	
Etiology of uveitis; n eyes (%)			-
• Idiopathic	44 (38.0)	59 (51.0)	
• Tuberculosis hypersensitivity	22 (19.0)	17 (15.0)	
• SLE	11(9.0)	-	
• Behcet's syndrome	15 (13.0)	17 (15.0)	
• Sarcoidosis	8 (7.0)	12 (10.0)	
• ANCA positive	3 (2.4)	3 (2.0)	
• Antiphospholipid syndrome	2 (2.0)	-	
• Multiple sclerosis	2 (2.0)	4 (3.0)	
• Leukocytoclastic vasculitis	2 (2.0)	-	
• Dermatomyositis	2 (2.0)	-	
• Takayasu arteritis	2 (2.0)	1 (1.0)	
• Syphilis/VZV	1 (0.8)	2 (2.0)	
• Rheumatoid arthritis	1 (0.8)	1 (1.0)	

N, number; IQR, Interquantile range; LogMAR, Logarithm of the minimum angle of resolution; IU, Intermediate uveitis; PU, Posterior uveitis; PANU, Panuveitis; ANCA, Antinuclear cytoplasmic antibodies. HIV, Human immune deficiency virus, HZV, Herpes zoster virus.

* The p-value was calculated using Mann-Whitney test for continuous variables and Pearson Chi-square test for categorical variables

Table 3

Table 3 Risk factors for vision loss in ischemic and non-ischemic vasculitis

Factors	IRV				Non-IRV			
	Crude		Adjusted		Crude		Adjusted	
	HR (CI)	P	HR (CI)	P	HR (CI)	P	HR (CI)	P
Cataract	1.45 (0.5-4.1)	0.47	-	-	1.38 (0.6-3.2)	0.46	-	-
Macular edema	1.40 (0.6 – 3.0)	0.38	2.5 (1.08-5.7)	**0.03**	1.67 (0.8-3.5)	0.18	1.64 (0.6-4.0)	0.27
Retinal detachment	2.0 (0.26-15.1)	0.49	-	-	6.8 (1.5-29.5)	**0.01**	-	-
Non-infectious	0.22 (0.06-0.75)	**0.01**	0.5 (0.1-1.9)	0.34	4.76 (1.8-12.1)	**0.001**	2.72 (0.9-7.9)	0.06
Ischemic Index	1.01(0.9-1.0)	0.50	-	-	-	-	-	-
Macular ischemia	7.8 (3.6 – 17.1)	**<0.001**	9.2 (3.9-21.6)	**<0.001**	-	-	-	-
Vitreous hemorrhage	1.51 (0.6 – 3.3)	0.30	-	-	-	-	-	-
NV	0.95 (0.4 – 2.3)	0.91	-	-	-	-	-	-
Systemic prednisolone	0.35 (0.15 – 0.80)	**0.01**	0.33 (0.14-0.77)	**0.01**	0.26 (0.1-0.7)	**0.01**	0.19 (0.04-0.8)	**0.02**
Use of immune-suppressants	1.05 (0.5 – 2.2)	0.89	-	-	1.01 (0.40-2.5)	0.98	-	-

IRV, Ischemic retinal vasculitis; HR, Hazard ratio; CI, Confidence Interval

Table 4 Risk of neovascularization following diagnosis of retinal ischemia and the risk of neovascularization relapse after initial retinal laser photocoagulation.

Variables	Neovascularisation requiring first laser photocoagulation		Relapse requiring second laser photocoagulation	
	HR (CI)	P value	HR (CI)	P value
Infectious versus non-infectious uveitis	1.4 (0.86 – 2.53)	0.15	1.54(0.54-4.5)	0.40
Ischemic index	0.99 (0.98 – 1.01)	0.78	1.01 (0.98 – 1.04)	0.26
Peripheral ischemia versus - Midperipheral - Posterior pole	 0.98 (0.40 – 2.3) 1.34 (0.44 – 4.1)	 0.96 0.59	 1.7 (0.33-9.2) 1.03 (0.27 – 3.8)	 0.49 0.96
Ischemia involving ≥2 quadrants	2.70 (1.3 – 5.5)	**0.003**	0.81 (0.27 – 2.39)	0.7
Active uveitis at time of neovascularisation diagnosis	1.42 (0.83-2.41)	0.19	0.80 (0.26 – 2.47)	0.70
On systemic anti-inflammatory medications at time of neovascularisation diagnosis	1.13 (0.67-1.91)	0.62	1.56 (0.48 – 4.99)	0.43

HR, Hazard ratio; CI, Confidence Interval

Table of content statement

Manuscript No: AJO-16-1631

Manuscript title: "*Clinical outcome of retinal vasculitis and predictors for prognosis of ischemic retinal vasculitis*

Comparison of clinical outcomes between eyes with retinal vasculitis and non-vasculitis found that the risks of vision loss and macular edema were worse in the vasculitis group. The rate of new vessels relapse in ischemic retinal vasculitis following first laser photocoagulation was 38.1%. The study also recommended to apply laser photocoagulation when ≥ 2 quadrants of retina are affected by capillary non-perfusion as this group carries a higher risk of new vessels formation.

Biosketch Lazha Sharief

Lazha Sharief obtained her PhD from the Institute of Ophthalmology at University College London (UCL) through a Kurdistan Regional Government scholarship. She is an awardee of the Fulbright Scholarship through which she obtained her MPH degree from the University of South Florida in U.S. She obtained her High Diploma (Master) degree in ophthalmology from Hawler Medical University. At present, she specializes in uveitis and works in the Department of Clinical Ophthalmology at Moorfields Eye Hospital in UK.

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