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Analysis of Predisposing Clinical Features for Worsening Traction After Treatment of Familial Exudative Vitreoretinopathy in Children

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• PURPOSE: To determine the incidence of worsening vitreoretinal traction after laser treatment for familial exudative vitreoretinopathy (FEVR) and to determine whether any baseline clinical features are associated with worsening.

• DESIGN: Retrospective cohort comparison study in a university tertiary referral center. Methods: All patients 0-21 years of age treated with laser from January 1, 2001, to June 1, 2018, were studied. Worsening traction after treatment was defined as the occurrence within 6 months of worsening or development of tractional retinal detachment, folds, dragging, breaks, rhegmatogenous detachment, or worsening tractional membranes. Comparisons of baseline features between groups with and without worsening were performed to determine features associated with higher risk.

• RESULTS: A total of 46 eyes from 28 patients met inclusion criteria. Of the 46 eyes, 6 (13%) had worsening after treatment. There were no significant differences in age or other baseline demographics between the cohorts with and those without worsening traction. The presence of proliferative tissue in contact with the lens was found in 2 of 6 patients with worsening compared to 1 of 40 (3%) without worsening ($P = .04$). Mean follow-up was 57.8 months (range, 6.6-134 months). At the 6-month follow-up, median logMAR visual acuity in the cohorts with and without worsening was 1.7 (Snellen 20/1002; n = 5) and 0.24 (Snellen 20/35; n = 16), respectively.

• CONCLUSIONS: Laser treatment resulted in worsening traction in a substantial proportion of eyes with FEVR. Children with proliferative tissue in contact with the lens may be at higher risk of worsening after laser. Potential measures to reduce risk will require further study to establish efficacy. (Am J Ophthalmol 2021;223:430–445. © 2020 Elsevier Inc. All rights reserved.)

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FAMILIAL EXUDATIVE VITREORETINOPATHY (FEVR) was first described by Criswick and Schepens in 1969.[1] It is a congenital, bilateral, proliferative retinopathy that has a clinical appearance similar to retinopathy of prematurity (ROP), but it is found in full-term children.[2,3] The condition is characterized by peripheral avascular retina with neovascularization often growing at the vascular-avascular junction.[4–6] Subretinal yellow exudates, vitreous hemorrhage (VH), fibroglial proliferation, retinal dragging, retinal folds, and retinal detachment are hallmarks of the condition.[7–12] White lesions and exudates on the surface of the retina have been described in some cases of FEVR.[13–15] Over time, some cases may show progressive worsening, but episodes of exudation and proliferation can be separated by years of stable inactivity.[10] Staging systems based on the clinical features noted above have been devised.[2,12,16,17] Several genetic mutations have been described in FEVR families, and inheritance can be autosomal recessive, autosomal dominant, or X-linked recessive.[18–20] Many of the known mutations are involved in the Wnt-receptor β-catenin signaling pathway.[21] Interruption of this pathway likely explains the arrest of retinal vasculardevelopment in the periphery with resulting ischemia and production of vascular endothelial growth factor (VEGF). Treatment consists of some combination of peripheral retinal ablation with laser or cryotherapy,[11,16] injection of intravitreal anti-VEGF medications,[22–24] or, in cases with traction or rhegmatogenous retinal detachment (RD), scleral buckling (SB) and pars plana vitrectomy (PPV).[11,16,25–32]

FEVR is one of the more common causes of nontraumatic RD in children.[33,34] RD in FEVR patients may result from traction, exudation, or from a traction-induced retinal tear. The disease is often asymmetrical, and 1 eye commonly has severe vision loss by the time the condition is diagnosed. Therefore, the stakes for treatment of the second eye can be very high.

We hypothesize that some children with FEVR show worsening of vitreoretinal traction after laser treatment. In addition, we hypothesize that there are certain baseline clinical features that are associated with a higher risk for developing worsening traction after treatment. The aims

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of this study were to retrospectively evaluate a series of FEVR patients to determine the incidence of worsening vitreoretinal traction after laser ablation or anti-VEGF therapy and to determine whether there are particular clinical features that place patients at higher risk of developing worsening traction. Because there are no large series specifically studying the risk for worsening after treatment, this study adds substantial data for FEVR and may help guide treatment strategies in the future.

METHODS

• **STUDY DESIGN:** A retrospective cohort comparison study was performed in all pediatric patients with FEVR treated with laser ablation of the avascular retina and/or injections of intravitreal anti-VEGF agents at Emory Eye Center and Children's Healthcare of Atlanta between January 1, 2001, and June 1, 2018

Before initiating data collection, the Emory University institutional review board (IRB 00104958) approved this retrospective review of patients with a diagnosis of FEVR and treated at this institution. The study adhered to tenets of the Declaration of Helsinki and demonstrated compliance with the Health Insurance Portability and Accountability Act of 1996. Informed consent for the research use of the patient records was waived by the IRB, as the research was retrospective in nature and involved no more than minimal risk to the subjects. Informed consent for treatment was obtained from the families of all patients regarding the risks, benefits, and alternatives prior to administration of laser ablation or anti-VEGF therapy.

• **STUDY POPULATION:** Patients 21 years of age and younger with diagnoses of FEVR based on history, clinical examination, and imaging evaluation and had undergone treatment at Emory Eye Center or Children's Healthcare of Atlanta between January 1, 2001, and June 1, 2018, were included in the study

A computerized search for billing codes was used to identify patients with possible FEVR (Supplemental Table 1 for all International Classification of Diseases edition 9 and 10 [ICD-9 and -10] codes used in the study). Charts were reviewed, and patients with an incorrect diagnosis or an inaccessible encounter were excluded. Patients who had had prior treatments at other facilities were included only if they later received treatment in the form of laser photocoagulation or intravitreal anti-VEGF injections at the authors' institution. Other exclusion criteria consisted of inadequate follow-up (at least 3 months of follow-up from the time of first treatment) or age greater than 21 at the time of presentation or at the time of treatment. After inclusion and exclusion criteria were applied, 46 eyes from 28 patients were included in the final cohort for the study (Figure 1).

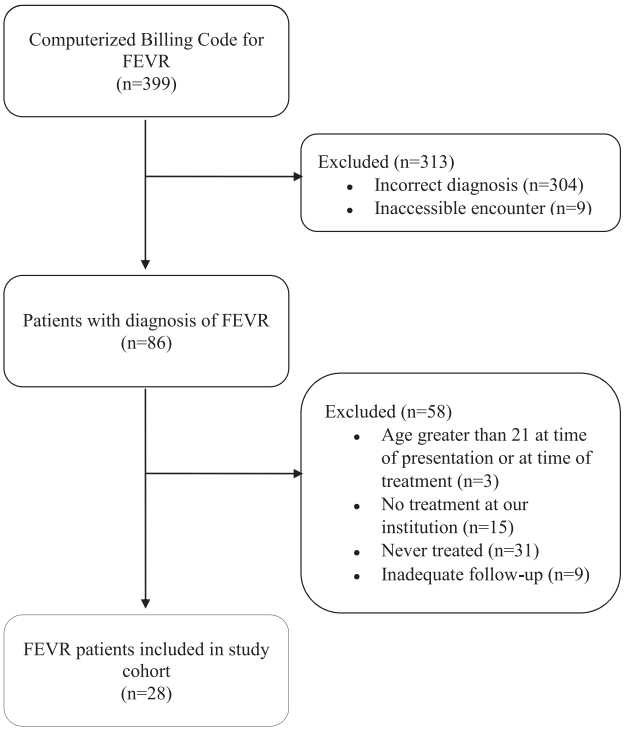

FIGURE 1. Flowchart of patients who met inclusion and exclusion criteria.

• **MEDICAL RECORD REVIEW:** Baseline data such as demographics (age and sex), laterality, family history, symptoms prior to presentation (strabismus, decreased vision, nystagmus), duration of symptoms prior to presentation, previous diagnoses, and prior treatment were collected

Ophthalmic evaluation including best-corrected visual acuity, intraocular pressure, lens status, status of exudates, and status of vitreoretinal traction were recorded based on slit lamp and dilated funduscopic examinations documented in their medical records. Visual acuity data were not obtained for some visits due to lack of patient cooperation or because examinations were performed with patients under anesthesia. For young patients requiring an examination under anesthesia, fundus photography and fluorescein angiography were performed using the RetCam3 wide-field digital imaging system (Clarity Medical Systems, Pleasanton, California). A Topcon TRC 50DX retinal camera (Topcon America, Oakland, New Jersey) or an ultrawide field imaging system, Optos (Optos, Marlborough, Massachusetts) were used in patients who could tolerate both color fundus photography and fluorescein angiography in clinic. Treatments in the form of laser photocoagulation, intravitreal anti-VEGF injections, or surgical intervention were recorded, as were the timing of treatments and ophthalmic evaluations at the time of each treatment. Classification of retinal status by stage was determined based on the updated FEVR clinical staging system described by Kashani and associates[17]

TABLE 1. Demographics and Baseline Clinical Features of Eyes With and Without Worsening Traction After Treatment of Familial Exudative Vitreoretinopathy

	No Worsening Traction (n = 40)	Worsening Traction (n = 6)	*P* Value
Sex, n (%)			
Females	20 (50)	4 (67)	.67
Males	20 (50)	2 (33)	
Median age, y (first quartile [q1], third quartile [q3])	5.27 (1.32, 9.74)	4.77 (3.31, 6.2)	.83
Family history, n (%)			
No	28 (70)	5 (83)	.62
Unknown	4 (10)	1 (17)	
Yes	8 (20)	0 (0)	
Symptoms noted by, n (%)			
Patient	6 (15)	0 (0)	.50
Parent	22 (55)	6 (100)	
Referring Physician	6 (15)	0 (0)	
Unknown	6 (15)	0 (0)	
Symptoms, n(%)			
Strabismus	14 (35)	4 (67)	.57
Decreased vision	11 (28)	2 (33)	
Positive family history	2 (5)	0 (0)	
Nystagmus	2 (5)	0 (0)	
Other or N/A	11 (28)	0 (0)	
Kashani stage at initial examination, n (%)			
1A	12 (30)	0 (0)	.26
1B	1 (3)	0 (0)	
2A	18 (45)	3 (50)	
2B	5 (13)	1 (17)	
3A	1 (3)	0 (0)	
3B	1/40 (3)	1/6 (17)	
4A	1/40 (3)	0/6 (0)	
4B	1/40 (3)	1/6 (17)	

(Supplemental Table 2). Briefly, stage 1 disease represents only avascular peripheral retina and is almost always diagnosed by using fluorescein angiography. Stage 2 disease represents an avascular retina with (Table 1, 2B) or without (Table 1, 2A) the clinical appearance of exudate or the angiographic appearance of leakage in the late phase. Stage 3 disease represents macula-sparing retinal detachment that is tractional or exudative (commonly a combined mechanism). Stage 3A lacks any clinical signs of exudation, or leakage on angiography, whereas stage 3B (Table 1) has exudation or leakage. Stage 4 disease represents macula-involving retinal detachment that is tractional or exudative and is also annotated as 4A or 4B (Table 1) depending on the presence of exudation or angiographic leakage. Stage 5 disease represents total retinal detachment and is annotated as 5A or 5B (Table 1) depending on whether the detachment has an open or closed funnel configuration.[17]

• **ASSESSMENT OF WORSENING TRACTION:** Clinical assessment of worsening traction was determined at each follow-up visit based on the slit lamp examination and dilated funduscopic examinations documented in the medical records at each visit and compared to the prior visit

The status of worsening traction after treatment was defined as the occurrence within 6 months after the most recent treatment of any of the following: worsening or development of tractional retinal detachment; worsening or development of dragging; worsening or development of folds; worsening vitreous membranes exerting traction on the retina; development of retinal breaks; or the development of a rhegmatogenous retinal detachment. Worsening traction that developed greater than 6 months after treatment was presumed to be secondary to natural progression of disease. For patients with worsening traction after treatment, the timing of onset of worsening traction after treatment was recorded. The treatment session prior to the onset of worsening traction was defined as the "causative treatment." Ophthalmic evaluation as described above was collected at the initial visit, first treatment visit, or causative treatment visit, and subsequent visits at months 1, 3, 6, 9, 12, and 24, and at the final follow-up visit. Not all eyes underwent examinations in the office or with the patient under anesthesia at each of the specified time points.

• **OUTCOME MEASUREMENTS:** The main outcome measurements were the incidence of worsening traction after

TABLE 2. Total Number of Treatments In Eyes Without And With Worsening Traction After Treatment

Treatment	Number of Treatments	No Worsening Traction (n = 40)	Worsening Traction (n = 6)
Laser, n (%)			
	1	22 (55)	3 (50)
	2	13 (33)	1 (17)
	3	4 (10)	1 (17)
	4	1 (3)	1 (17)
Pars plana vitrectomy, n (%)			
	0	34 (85)	0 (0)
	1	5 (13)	3 (50)
	2	1 (3)	2 (33)
	3	0 (0)	1 (17)
Scleral buckle, n (%)			
	0	38 (95)	2 (33)
	1	2 (5)	4 (67)
Anti-VEGF, n (%)			
	0	35 (88)	6 (100)
	1	1 (3)	0 (0)
	2	1 (3)	
	4	1 (3)	
	5	1 (3)	
	9	1 (3)	

VEGF = vascular endothelial growth factor.

treatment. To determine whether there were certain clinical features that predisposed patients to worsening traction after treatment, data were collected for the following pretreatment clinical features: presence of retinal exudates, vitreous blood, subretinal blood, avulsed retinal vessels, sheets or strands of condensed vitreous, tractional RD, exudative RD, radial retinal fold, circumferential retinal fold, white fibroglial proliferative tissue, and proliferative tissue in contact with the lens. For patients who demonstrated worsening traction after treatment, these clinical features were recorded for the ophthalmic evaluation prior to the causative treatment. For patients who did not have worsening traction after any treatment, the presence of these clinical features was assessed prior to each treatment session and was collectively recorded.

• **STATISTICAL ANALYSIS:** Statistical analyses were performed using SAS version 9.4 software (Cary, North Carolina). A chi-squared test (or Fisher exact test when necessary) was used to statistically evaluate differences in proportions of pretreatment clinical features between the cohort with and those without worsening traction. *P* values of less than .05 were considered statistically significant

For visual acuity outcomes, visual acuity was converted to logarithm of the minimum angle of resolution (logMAR) equivalents when possible and was examined descriptively using medians and interquartile ranges at all available time points for the first year of follow-up. Some visual acuity measurements were excluded from the analysis, as they were unable to be converted to logMAR equivalents. These measurements included the following: blink to light, fix and follow, no fix and follow, central-steady-maintained, light perception, and no light perception. Additionally, these visual acuity measurements were categorized and examined descriptively as well.

RESULTS

• **PATIENT CHARACTERISTICS:** A total of 46 eyes from 28 patients met the inclusion criteria for this study. Eighteen of these patients underwent treatment to both eyes at the authors' institution. Of the 28 patients, 14 (50%) were female and 4 (14%) reported a family history of FEVR. The mean age at presentation was 6.6 ± 5.5 years. Symptoms that prompted evaluation included strabismus in 10 patients (36%), decreased vision in 10 patients (36%), positive family history in 1 patient (3.6%), nystagmus in 1 patient (3.6%), and other in 6 patients (21%). These symptoms were noted by the parent in 17 patients (61%), by the patient themselves in 4 (14%), were elicited by the referring physician in 3 (11%), and in 4 (14%) cases. The person who detected symptoms was not recorded. Of the 46 treated eyes, 6 eyes (13%) of 6 patients had worsening of traction after treatment, and 40 (87%) showed no worsening of traction after treatment. There were no significant differences between the sexex, median ages, family

TABLE 3. Clinical Features of Patients With Worsening Traction after Treatment

Case/Sex	Age (y)	Eye	Family History	Treatments Prior to Causative Treatment	Causative Treatment	Stage at Time of Causative Treatment	Clinical Features At Time of Causative Treatment	Length of Time Until Worsening Traction	Stage After Treatment	Total Treatments Performed
1/F	6.3	Right	Unknown	Laser × 3	Laser	3B	Subretinal exudates, preretinal hemorrhage, sheets and strands of condensed vitreous, peripheral TRD, white fibroglial tissue	4 days	5A	Laser × 4, PPV/MS, SB/PPV/SO, PPV/PPL/SOR
2/F	6.1	Right	No	None	Laser	4B	macula-involving TRD, extensive subretinal exudates, circumferential fibrotic ridge	3 weeks	4B	Laser × 1, PPV/MS
3/F	3.3	Right	No	Laser × 1	Laser	3B	peripheral exudative retinal detachment, sheets and strands of condensed vitreous, subretinal exudates, white fibroglial tissue	19 days	4B	Laser × 2, SB/PPV/SO, PPV/lensectomy, capsulectomy/SO reposition
4/M	7.0	Right	No	None	Laser	2B	radial retinal folds, avulsed vessel extending inferiorly, fibrous tissue touching lens	7 weeks	4A	Laser × 1, PPV/SB/MS/lensectomy/PFO/EL/FAX/SO
5/F	3.4	Left	No	None	Laser	2B	radial retinal fold, white fibroglial tissue	3 months	4B	Laser × 1, SB/PPV/MS/FAX
6/M	1.5	Right	No	Laser × 1	Laser	2A	retinal tear, white fibrous tissue touching lens	6 months	2A	Laser × 3, PPV/EL/SO, PPV/SOR

EL = endolaser; F= female; FAX = fluid-air exchange; M = male; MS = membrane stripping; PFO = perfluoro-n-octane heavy liquid; PPL = pars plana lensectomy; PPV = pars plana vitrectomy; SB = scleral buckle; SO = silicone oil; SOR = silicone oil removal; TRD = tractional retinal detachment.

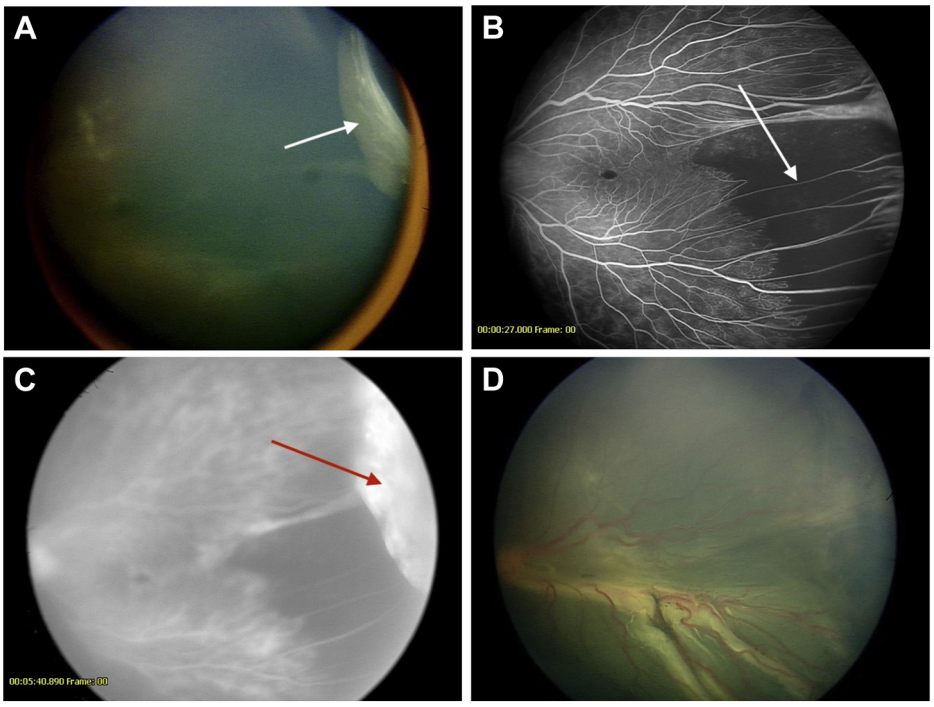

FIGURE 2. (A) Left eye of Patient 5 showing white fibroglial tissue (arrow) in the far temporal periphery, taken with scleral depression while the patient was under anesthesia. (B) Mid-phase fluorescein angiography showing avascular retina with large vessels spanning the avascular zone (arrow) and entering the far temporal white fibroglial tissue. (C) Late-phase fluorescein angiogram showing staining of the white fibroglial tissue (arrow) in the far periphery, taken with scleral depression. (D) 3 months after laser treatment, administered at the time the other views were taken. The left eye was found to have combined traction and rhegmatogenous total retinal detachment. Exposure and contrast were digitally enhanced for the photographs in this figure. Data for all patients in the study is shown in Supplemental Table 3.

histories, symptoms, or Kashani stages of eyes with worsening traction after treatment compared to those without worsening traction after treatment (Table 1). The mean follow-up time was 57.8 months (range, 6.6-134 months).

• **TREATMENTS:** Of the 6 eyes with worsening traction after treatment, all received laser therapy, none received anti-VEGF therapy, all underwent PPV, and 4 of 6 underwent SB. In this group, the PPVs and SBs were performed to address the worsening traction after laser. Of the 40 eyes without worsening traction after treatment, 40 eyes (100%) received laser treatment, 5 (12.5%) received anti-VEGF therapy, 6 (15%) underwent PPV, and 2 (5%) underwent SB at some point during their treatment courses. A total of 9 operations (PPVs or SBs) were performed in 7 eyes in the group without worsening traction after laser. None of these 9 operations were performed to address traction that occurred after laser. Three eyes presented with severe disease requiring SB or PPV as the initial treatment. These eyes had subsequent laser treatments without worsening traction within 6 months. One of these patients had SB as the initial treatment due to severe combined tractional RD and rhegmatogenous RD. This eye eventually underwent PPV 4 years after the most recent laser treatment. Two eyes presented with a visually significant epiretinal membrane requiring PPV and membrane peel, with 1 eye requiring an additional PPV 5 months later for recurrent epiretinal membrane. Neither of these eyes had worsening traction after laser treatment. Two eyes had worsening of disease occurring greater than 6 months after laser and were, thus, according to the authors' methodology, deemed to have worsening traction as a result of natural history and not as a result of treatment. One of these eyes was lost to follow-up for 5 years and presented with a severe tractional RD requiring PPV 7 years after the most recent laser treatment, and the other eye developed VH requiring PPV 8 months after the most recent laser therapy. Table 2 displays the total number of treatments between the cohorts with and without worsening traction after treatment.

• **CASES WITH WORSENING TRACTION AFTER TREATMENT:** Of 46 eyes treated with laser, 6 eyes (13%) of 6 patients developed worsening traction after treatment (Table 3). Of the 6 patients with worsening, 4 were female, and 2 were male. None had a known family history of FEVR. The median age at presentation was 4.77 years (range, 1.49-6.98 years). The causative treatment was laser photocoagulation in all 6 eyes. At the time of the causative treatment, the Kashani stage was 2A in 1 patient, 2B in 2 patients, 3B in 2 patients, and 4B in 1 patient (Table 1). Pretreatment clinical features included the presence of

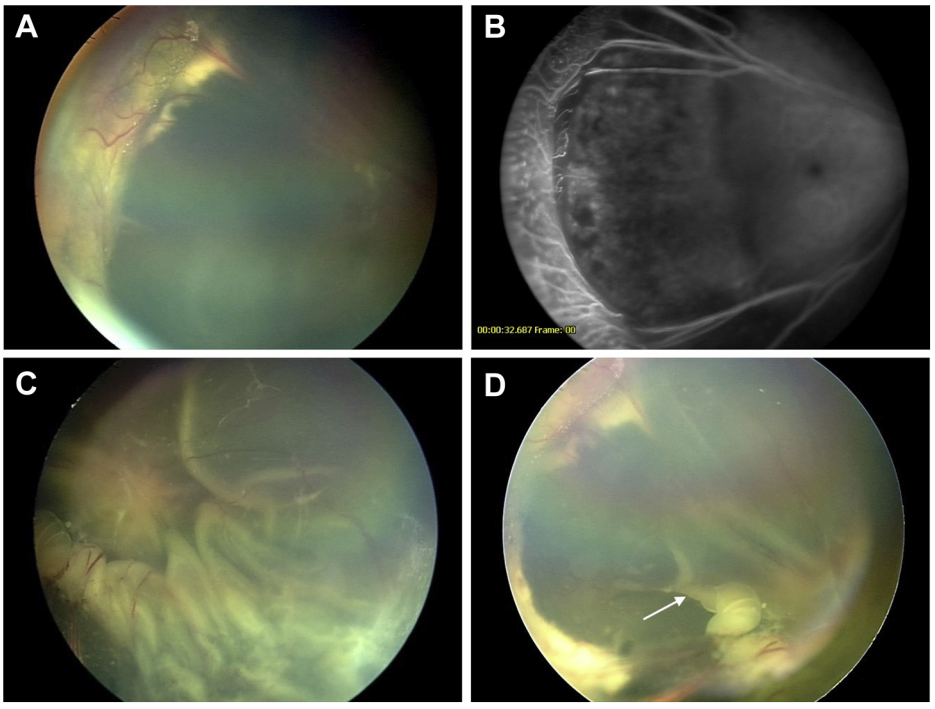

FIGURE 3. (A) Extensive subretinal yellow exudates under the far temporal peripheral retina of the right eye of Patient 3. (B) Fluorescein angiography shows temporal dragging and abnormal retinal vessels overlying the area with subretinal exudates. (C) Total combined traction and rhegmatogenous retinal detachment developed 19 days after laser treatment performed on the day the first photographs were taken. (D) A large retinal tear is seen temporally (arrow). Exposure and contrast were digitally enhanced for the photographs in this figure.

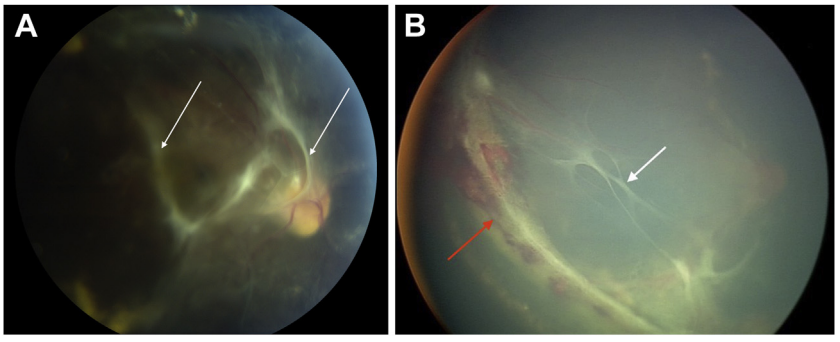

FIGURE 4. (A) Strands of condensed vitreous (arrows) can be seen over the posterior pole in the right eye of Patient 1. (B) Similar strands are seen temporal to the optic disc (white arrow) in the right eye of Patient 2. In addition, Patient 2 has a thick temporal elevated fibrotic ridge oriented circumferentially with overlying preretinal blood and associated traction retinal detachment (red arrow). Exposure and contrast were digitally enhanced for the photographs in this figure.

white fibroglial tissue in 4 (Figure 2), subretinal exudates in 3 (Figure 3), strands of condensed vitreous in 2 (Figure 4), tractional retinal detachment in 2, radial fold in 2 (Figure 5), proliferative tissue in contact with the lens in 2 (Figure 5), preretinal blood in 1, avulsed vessels in 1, exudative retinal detachment in 1, and circumferential fold in 1. Worsening traction after laser manifested as worsening tractional RD in 2, formation of retinal break in 1, and onset of combined tractional and rhegmatogenous RD in 3 eyes. The median length of time until the development of worsening traction was 35 days (range, 4 days to 6 months). All 6 patients underwent surgical intervention in the form of PPV and/or SB to treat the manifestations of worsening traction.

• **CLINICAL FEATURES PREDISPOSING TO WORSENING TRACTION AFTER TREATMENT:** Pretreatment clinical features were assessed to determine whether there were certain

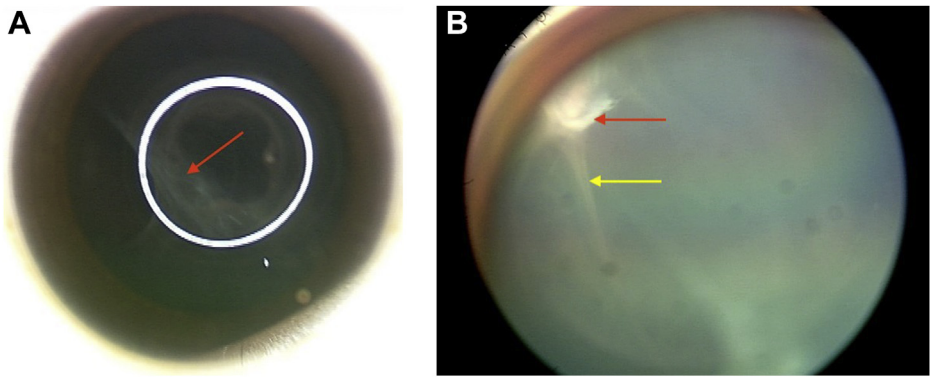

FIGURE 5. Proliferative tissue in contact with the lens is seen in the right eye of Patient 4 (red arrows). (A) Viewed from the anterior segment. (B) Viewed from the posterior segment. A radial fold of retina can be seen extending posteriorly from the proliferative tissue (yellow arrow). The edge of the iris is also visible in the upper left portion of the photograph. Exposure and contrast were digitally enhanced for the photographs in this figure.

TABLE 4. Pretreatment Clinical Features Present in Cohorts Without and With Worsening Traction After Treatment

Clinical Feature, n (%)	No Worsening Traction (n = 40)	Worsening Traction (n = 6)	*P* Value
Subretinal exudates	5 (13)	3 (50)	.06
Preretinal blood	2 (5)	1 (17)	.35
Vitreous blood	2 (5)	0 (0)	1.00
Subretinal blood	0 (0)	0 (0)	NA
Avulsed vessels	0 (0)	1 (17)	.13
Strands of condensed vitreous	3 (8)	2 (33)	.12
Tractional retinal detachment	3 (8)	2 (33)	.12
Exudative retinal detachment	1 (3)	1 (17)	.25
Radial ridge/fold	3 (8)	2 (33)	.12
Circumferential ridge/fold	1 (3)	1 (17)	.25
White fibroglial/proliferative tissue	25 (63)	4 (67)	1.00
Proliferative tissue in contact with lens/ retrolental plaque	1 (3)	2 (33)	.04

NA = not applicable.

clinical characteristics that predisposed patients to worsening traction after treatment (Table 4). The presence of proliferative tissue in contact with the lens, or a retrolental plaque was found in 2 of 6 patients with worsening traction after treatment compared to 1 of 40 patients without worsening traction after treatment, and the differences between the groups were statistically significant ($P = .04$). Another feature more weakly associated with worsening traction after treatment was the presence of subretinal exudates, which were found in 3 of 6 eyes with worsening traction and only 5 of 40 eyes without worsening traction ($P = .06$). Other pretreatment clinical features such as the presence of strands of condensed vitreous, tractional RD, and white fibroglial proliferative tissue, were not found to be significantly associated with worsening traction after treatment.

• **VISUAL ACUITY OUTCOMES:** Visual acuity outcomes were available for a subset of patients who were cooperative for visual acuity testing and who were not examined under anesthesia. Outcomes were categorized based on the proportion in each group that had visual acuities ≥20/40, between 20/50 and 20/200, and <20/200 at different follow-up time points (Table 5). At baseline, the median logMAR visual acuity was 0.3 (Snellen 20/40) in the cohort without worsening traction after treatment (n = 25), compared to 0.57 (Snellen 20/74) in the cohort with worsening traction after treatment (n = 4). Although the majority of patients (15 of 25; 60%) presented with a visual acuity ≥20/40 in the cohort without worsening traction, none of the patients in the cohort with worsening traction presented with visual acuity ≥20/40. At the 1-month follow-up visit, half of patients (2 of 4) in the worsening

TABLE 5. Visual Acuity Outcomes between Cohorts with and without Worsening Traction after Treatment

	No Worsening Traction				Worsening Traction			
	logMAR	Visual Acuity			logMAR	Visual Acuity		
Time Point, mo	Median IQR (q1, q3)	≥20/40	20/50-20/200	<20/200	Median (q1, q3)	≥20/40	20/50-20/200	<20/200
Baseline	0.30 (0, 1.0) (n = 25)	15/25 (60)	6/25 (24)	4/25 (16)	0.57 (0.54, 1.95) (n = 4)	0/4 (0)	3/4 (75)	1/4 (25)
1	0.51 (0.24, 0.90) (n = 24)	8/24 (33)	10/24 (42)	6/24 (25)	0.94 (0.48, 2.20) (n = 4)	0/4 (0)	2/4 (50)	2/4 (50)
3	0.51 (0.18, 0.60) (n = 14)	6/14 (43)	8/14 (57)	0/14 (0)	1.45 (0.89, 2.3) (n = 4)	0/4 (0)	1/4 (25)	3/4 (75)
6	0.24 (0.10, 0.62) (n = 16)	9/16 (56)	5/16 (31)	2/16 (13)	1.7 (1.4, 3.0) (n = 5)	0/5 (0)	1/5 (20)	4/5 (80)
9	0.34 (0.09, 1.15) (n = 8)	5/8 (63)	2/8 (25)	1/8 (13)	1.17 (0.48, 1.48) (n = 3)	0/3 (0)	1/3 (33)	2/3 (67)
12	0.44 (0.14, 0.67) (n = 20)	9/20 (45)	9/20 (45)	2/20 (10)	1.09 (0.70, 1.48) (n = 2)	0/2 (0)	1/2 (50)	1/2 (50)

IQR = interquartile range; q1 = first quartile; q3 = third quartile; logMAR = logarithm of the minimum angle of resolution; mo = months.

traction cohort had a visual acuity <20/200, whereas only 6 of 24 patients (25%) without worsening traction had a visual acuity <20/200. At 6 months, this trend persisted, as the proportion of patients who had a visual acuity <20/200 in the groups with and without worsening traction was 4 of 5 (80%) and 2 of 16 (13%), respectively. Meanwhile, the proportion of patients in whom visual acuity ≥20/40 was maintained at 6 months was 9 of 16 (56%) in the cohort without worsening traction compared to none in the cohort with worsening traction. At the 1-year follow-up, the median logMAR visual acuity in the cohorts with and without worsening traction was 1.09 (Snellen 20/246; n = 2) and 0.44 (Snellen 20/55; n = 20), respectively. In the cohort without worsening traction, visual acuity ≥20/40 was maintained in 9 of 20 eyes (45%), and only 2 of 20 eyes (10%) had a visual acuity <20/200 at 1 year. In contrast, at this time point in the cohort with worsening traction, none had visual acuity ≥20/40, and half had a visual acuity <20/200. The median logMAR visual acuity was worse in the cohort with worsening traction after treatment than in the cohort without worsening traction after treatment at all time points (Figure 6).

• **RETINAL STATUS OVER TIME:** To investigate changes in retinal status over time, the Kashani stage at each follow-up visit was categorized as "better", "same", or "worse" compared to the baseline stage (Figure 7). Using Kashani and associates' revised FEVR staging system,[17] the higher staging numbers were stipulated as "worse," and stages with exudation or leakage (B, Table 1) were characterized as worse than stages without exudation or leakage (Table 1, A). For example, stage 4A was characterized as worse than stage 3B (Table 1), and stage 3B (Table 1) was characterized as worse than stage 3A (Table 1).

Worsening Kashani stage at 1 month was seen in 3 of 5 versus 3 of 31 in the cohorts with and without worsening traction, respectively. At 3 months, most eyes in both cohorts were classified as the same Kashani stage as baseline (3 of 5 in the cohort with, compared to 18 of 27 in the cohort without worsening traction). A similar pattern was observed at the 6-month follow-up, with both groups showing most patients in the same Kashani stage as baseline. By 9 months, a greater proportion of patients achieved a better stage in the cohort with initial worsening (2 of 3) compared to the cohort without worsening (4 of 14; 29%), likely due to surgical interventions that were performed to treat the worsening traction. At 12 months, compared to baseline, 2 of 4 patients in the group with initial worsening of traction had better Kashani stage, whereas only 4 of 26 (15%) in the cohort without initial worsening had a better Kashani stage.

DISCUSSION

THIS STUDY FOUND THAT A SIGNIFICANT PROPORTION OF eyes treated with laser for FEVR (6 of 46; 13%) had worsening vitreoretinal traction within 6 months of treatment. We analyzed Analysis of pretreatment clinical characteristics found 2 features that were associated with worsening after treatment. These were the presence of proliferative tissue in contact with the posterior capsule of the lens (retrolental fibrous plaque) and the presence of subretinal yellow exudates. Worsening of traction after treatment manifested as tractional RD (2 eyes), formation of retinal break (1 eye), or combined tractional and rhegmatogenous RD (3 eyes).

In reviewing studies of treatment of FEVR, there is ample evidence from previous studies that eyes may have worsening vitreoretinal traction after laser, cryotherapy, or anti-VEGF injections. However, to the present authors' knowledge, no studies have specifically examined the clinical features associated with worsening after treatment or the incidence of this phenomenon. The tendency of some FEVR patients to have worsening traction after treatment deserves more study and should be emphasized more clearly in the medical literature. To gain perspective on what has been written previously about worsening traction

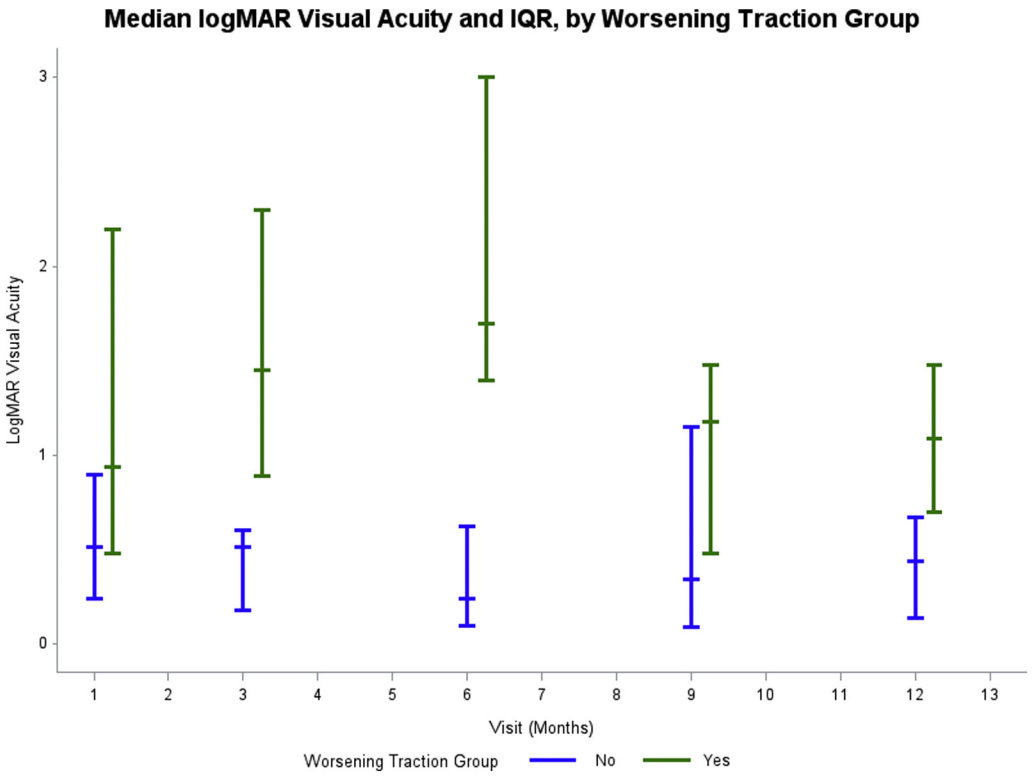

FIGURE 6. Median logMAR visual acuity and interquartile range by groups with and without worsening traction.

after treatment, all studies were reviewed that described outcomes of treatment of FEVR with laser, cryotherapy, or anti-VEGF injections. This review paid special attention to data regarding worsening traction after treatment.

In 2018, Lu and associates[24] reported generally favorable results of intravitreal ranibizumab (IVR) in a series of 37 eyes with FEVR. Their conclusion was that "IVR may be an effective modality in the treatment of FEVR." However, 19% of patients (7 of 37) required surgical intervention with PPV or SB for "persistent retinal neovascular activities and retinal traction" after IVR.[24] Presumably the 7 patients requiring surgical intervention had worsening traction that was either caused by the injection or that progressed despite the injection.

Also, in 2018, Takahashi and associates[35] reported results of surgical treatment for progressive fibrous tissue extending to the posterior retina in 4 eyes with FEVR. Traction RD and progressive macular dragging responded to vitrectomy with or without SB in all 4 cases. Before onset of traction, 2 of the 4 eyes were treated with laser ablation of the avascular peripheral retina. Worsening occurred shortly after laser in 1 case and 6 years after laser in the other case.

In 2017, Hocaoglu and associates[31] reported a series of 10 eyes (9 patients) undergoing vitrectomy for advanced FEVR performed by a single surgeon in Turkey. Stages 3, 4, and 5 FEVR were present in 4, 4, and 2 eyes, respectively. Three eyes (30%) had undergone laser photocoagulation 2-24 months before vitrectomy. None of the other eyes had been treated with laser, cryotherapy, or anti-VEGF injections. It is unknown how many FEVR eyes were treated with laser during the study period that did not worsen after laser treatment. Two of the 3 laser-treated eyes developed rhegmatogenous RD after laser, and vitrectomy was prompted in the third laser-treated eye by worsening of traction without rhegmatogenous RD. The possibility that laser might have been a cause for worsening traction in these eyes was not discussed in that paper.

In 2015, Henry and associates[36] reported 13 eyes of 11 patients treated with intravitreal bevacizumab for FEVR. Three of those 13 eyes (23%) had rapid progression of tractional RD shortly after administration of intravitreal bevacizumab. The authors hypothesized that worsening traction resulted when extensive neovascularization underwent fibrotic transformation leading to the development of tractional retinal detachment following treatment.[36]

An article by Yamane and associates[29] from 2014 reviewed results of surgical intervention for 31 eyes with tractional RD from FEVR.[29] Five of those eyes had undergone laser photocoagulation at an outside facility before being referred for RD. The authors recommended that laser alone never be applied when tractional RD exists. In their series, if photocoagulation was applied, as it was in 23 of 31 eyes, it was done in conjunction with SB or PPV. An earlier

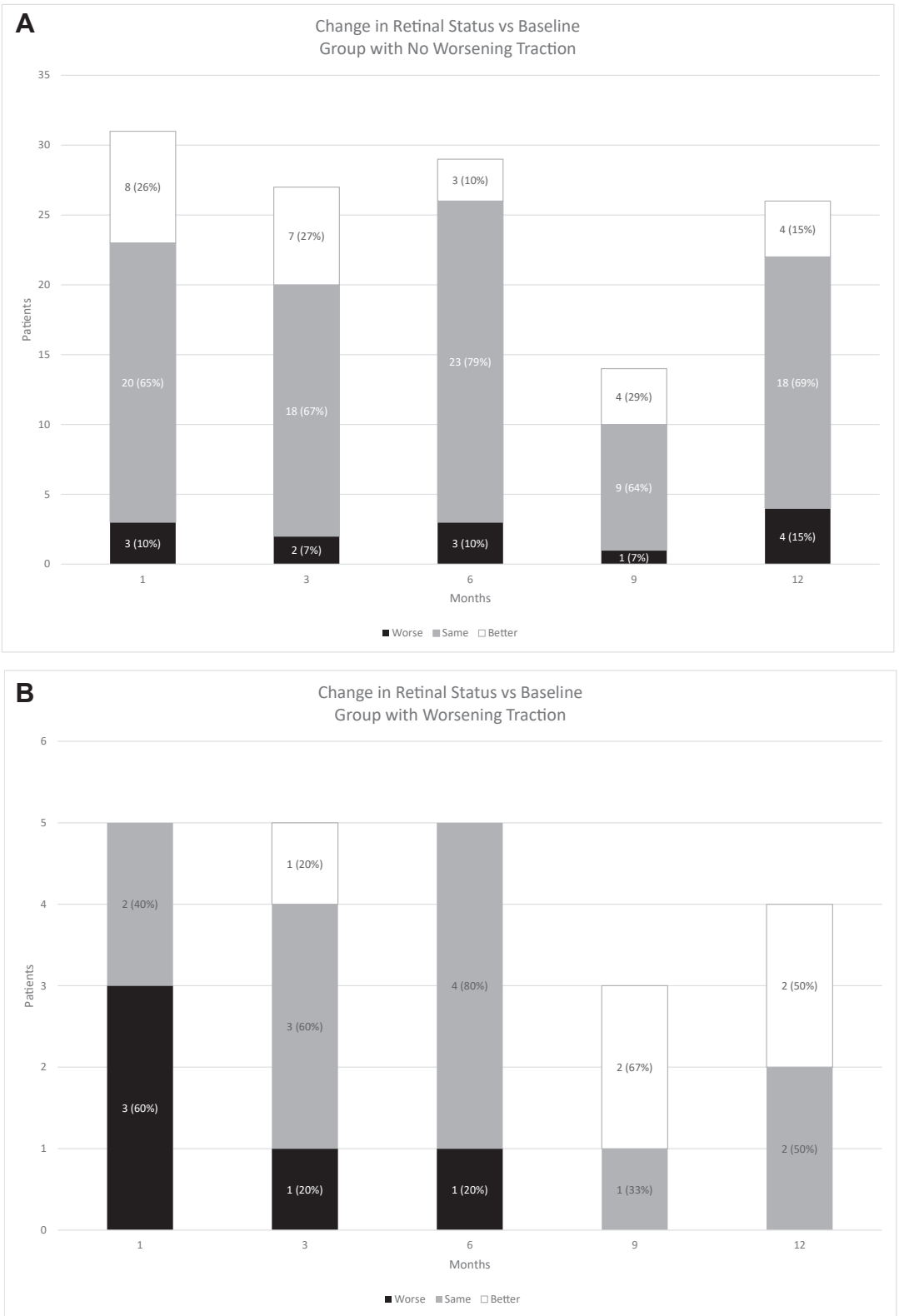

FIGURE 7. Change in retinal status over time by Kashani stage compared to baseline in cohorts with (A) and without (B) worsening traction after treatment.

publication from the same institution examined the clinical features of congenital retinal folds, most of which were due to FEVR.[37] The authors describe progressive fibrovascular proliferation in 10 eyes. Despite intervention with laser (4 eyes), PPV with lensectomy (5 eyes), and SB (1 eye), 2 of 10 treated eyes (20%) progressed to retinal detachment.[37] The authors do not comment about whether the progressive traction in those 2 eyes occurred as a result of laser-induced contraction of fibrosis.

In 2008, Quiram and associates[22] reported a series of 4 patients (4 eyes) with vascularly active FEVR treated with the anti-VEGF medication pegaptanib (Macugen).[22] Before the anti-VEGF injection, all 4 patients demonstrated increasing subretinal exudation despite previous treatment with laser photocoagulation, cryotherapy, and/or intravitreal steroid injections. All 4 patients had a decrease in exudation after treatment with anti-VEGF, but 2 of the 4 required vitrectomy for worsening vitreoretinal traction 2 to 3 months after the injection. The authors hypothesized that the rapid resolution of subretinal exudation or upregulation of transforming growth factor β levels may have contributed to the mechanism of worsening traction.

In 2004, Margolis and associates[38] reported a 17-month-old female with stage 2A (Table 1) FEVR treated in both eyes with laser photocoagulation to avascular retina. After laser treatment, the left eye stabilized and regressed, but the right eye showed progressive worsening of traction with development of a macular fold. The authors comment that FEVR can have a broad spectrum of treatment response and that FEVR does not always respond like ROP when avascular retina is treated with laser. They emphasize the possibility of disease progression despite appropriate laser therapy.

In 2003 Shukla and associates[11] reported a large series from India of 61 patients (116 eyes). As part of this series, 20 eyes underwent either laser treatment (15 eyes) or cryotherapy (5 eyes) as prophylaxis against the progression of RD. The age for these cases ranged from 9 to 55 years. Four patients were lost to follow-up, and the other 16 were reported to stabilize with no mention of worsening traction or progression of disease after treatment during a mean follow-up of 16.4 months (range, 2-40 months).

Pendergrast and Trese[16] reported results of surgical management of FEVR in 1998. Among the 52 eyes in the series were 15 eyes of 12 patients who underwent laser photocoagulation as the initial treatment. Of these 15 eyes treated with laser, 7 (47%) ultimately required SB or PPV. Six of the 7 who required SB or PPV had some degree of RD before the laser treatment. The purpose of the laser treatment in these cases was "to attempt to induce regression of extraretinal vascularization and reduce the amount of subretinal exudate before PPV."[16] However, at least 4 of these 7 eyes had worsening of traction after the laser. One patient started as stage 2B (Table 1) before laser and by 31 months after laser required PPV for stage 3B RD. Another patient started as stage 3B but progressed to total RD and underwent PPV 8 months later. Two eyes with stage 4 RDs had worsening traction after laser and required PPV 1 month and 5 months after laser. The other 3 eyes were either stage 3 or 4 at the time of laser, underwent SB or PPV, but no progression of the prelaser RD was reported. To summarize this series, 4 of 15 eyes (26.7%) treated with laser had progressive worsening of traction after treatment and required SB or PPV 1 to 31 months later.

In 1997 Shubert and Tasman[26] reported results of surgical intervention in 8 eyes (7 patients) with FEVR.[26] Seven of the 8 eyes had either tractional RD or rhegmatogenous RD, and 1 had VH on presentation. Initial treatments with cryotherapy, laser, SB, and PPV were performed at ages ranging from 6 months to 28 years (mean, 14.7 years) and retinal reattachment was achieved postoperatively in 6 of 8 patients. In Case 1, 2 cryotherapy treatments were applied to the right eye 6 years before onset of RD. In Case 5, a 1-year-old male, tractional RD developed soon after cryotherapy and was treated with SB. That eye was lost due to progressive traction despite PPV and SB revision. Case 5 also underwent cryotherapy in the left eye for retinal exudates, and the eye stabilized. Case 6 underwent laser photocoagulation in one eye and did well for 10 years until worsening traction and VH occurred at age 34. That patient stabilized with PPV. Overall, 4 of 8 eyes in that series were treated initially with cryotherapy or laser, and 3 of these 4 (75%) eventually had worsening of traction. One worsened soon after cryotherapy at age 1, and the others worsened at 6 years and 10 years after treatment.

In 1995, Benson[10] published a thesis on FEVR in which he studied 39 patients (78 eyes) of various ages and degrees of severity. Of the 39 patients, 9 (11 eyes) had neovascularization at the time of diagnosis and were treated with laser photocoagulation, cryotherapy, or vitreoretinal surgery. Despite those treatments, 7 of 11 eyes (63%) had final vision of counting fingers or worse. Nine eyes were initially treated with cryotherapy. Of those, 3 developed nonrhegmatogenous RDs, and a fourth eye developed rhegmatogenous RD within 1 year. A fifth case developed rhegmatogenous RD 7 years later. Time to onset of worsening was 1 month, 2 months, 4 months, 11 months, and 7 years. Two eyes were initially treated with laser. Both eyes stabilized initially, but 1 eye developed VH 6 years later and required vitrectomy. To summarize, 5 of 9 cryotherapy eyes (56%) had worsening traction after treatment. Neither of the 2 eyes initially treated with laser had worsening traction, but one developed VH years later.

Dudgeon[39] reported 2 family members who were treated with cryotherapy in 1979. Of the 3 eyes that were treated, 2 did well, but 1 developed total rhegmatogenous RD a few weeks after the treatment. In his discussion, Dudgeon emphasized the need for caution in considering prophylactic cryotherapy and said that when vitreous adhesions or traction are present, cryotherapy combined with SB may be preferable to cryotherapy alone.

Gow and associates[2] reported a family of 15 individuals affected by FEVR in 1971. Four eyes from those patients were treated with cryotherapy for dilated and tortuous vessels and subretinal exudates. Within 8-12 months of follow-up, all demonstrated atrophy of the fibrovascular cicatrix. No progression of traction was reported.

In Criswick and Schepens' original publication from 1969, 6 patients were presented and of the 12 eyes, 1 was blind and 11 had vision at the time of initial evaluation.[1] Nine of the 11 sighted eyes were treated with various combinations of cryotherapy, laser photocoagulation to abnormal vessels, and scleral buckling. The 2 untreated eyes with vision remained stable. However, all treated eyes showed either worsening over time or persistence of abnormal vessels in the treated area. The authors conclude that the "prognosis for complete arrest of the condition seems poor."[1]

In this review of all available studies of laser, cryotherapy, or anti-VEGF treatment for FEVR, studies were found that reported worsening traction after treatment at rates ranging from 0% to 75%. The review encompassed approximately 50 years and included patients with various ages and various degrees of disease severity. Thus, the ability to directly compare with the present series of laser-treated pediatric FEVR eyes is somewhat limited. Nevertheless, this review places the present rate at 13% with worsening of traction after treatment into broader context, and the present rate of worsening is generally consistent with those of other reports. Despite the strong tendency to have worsening after treatment in a substantial proportion of eyes treated for FEVR, the potential for worsening did not receive much attention in many of the previous publications on the subject. To the present authors' knowledge, there are no studies that specifically examined pretreatment clinical features that may be predictive of worsening traction.

How does the present rate of worsening traction after treatment of FEVR compare to other vasoproliferative conditions of the retina? In addition to FEVR, ablative treatments or anti-VEGF injections are widely used in the treatment of several proliferative retinopathies in both adults and children. Two conditions commonly treated with ablative therapy or anti-VEGF injections are proliferative diabetic retinopathy and ROP.[40,41] Like FEVR, worsening traction is known to occur after treatment in some cases of both ROP and proliferative diabetic retinopathy (PDR).

For ROP, worsening traction has been evaluated in large multicenter randomized trials of cryotherapy, laser, and anti-VEGF treatment. The Multicenter Trial of Cryotherapy for ROP (Cryo-ROP) randomized eyes with severe ROP to observation or to cryotherapy applied to peripheral avascular retina. The 3-month results were published in 1990 and showed unfavorable structural outcomes in 31.1% of treated eyes compared to 51.4% of control eyes.[42] The Early Treatment of ROP Trial (ETROP) evaluated laser for ROP and was published in 2003.[41] ETROP found unfavorable structural outcomes in 9.1% of laser treated eyes. For anti-VEGF therapy, the recently published Ranibizumab Versus Laser Therapy For The Treatment Of Very Low Birthweight Infants with ROP (RAINBOW) trial found unfavorable structural outcomes in 1.43% of the group receiving ranibizumab and 10% in the group undergoing laser therapy.[43] In all these ROP trials, unfavorable structural outcomes were defined as 1 of several manifestations of worsening fibrous traction, including a retrolental membrane obscuring the view of the posterior pole, temporal retinal vessel dragging with macular ectopia, posterior retinal fold involving the macula, and retinal detachment involving the macula.

For PDR, rates of worsening traction after laser and anti-VEGF have been evaluated in a large randomized clinical trial conducted by the Diabetic Retinopathy Clinical Research Network (Protocol S).[44] When worsening of traction as manifest by onset of TRD, rhegmatogenous RD, or progressive macular traction without RD were examined, rates of worsening traction were 6% versus 10% in the anti-VEGF group and laser group, respectively ($P = .08$).[44] An earlier paper by Arevalo and associates[45] reported worsening traction in PDR treated with bevacizumab at a rate of 5.2%.

To summarize major studies' rates of worsening traction after treatment, ROP rates have improved from approximately 30% with cryotherapy[42] to 10% with laser,[41,43] and more recently to 1.43% with anti-VEGF.[43] Proliferative diabetic retinopathy rates of worsening traction were 10% with laser and 6% with anti-VEGF.[44] As such, the present rate of worsening after treatment of FEVR (13%) was higher than modern treatments of ROP or PDR. However, it is notable that the present cases of worsening traction presented after laser treatment, and none had anti-VEGF therapy. Serial anti-VEGF therapy may possibly decrease the incidence of worsening traction in FEVR as observed previously in ROP and PDR; however, this hypothesis was not analyzed in the current study.

Reviewing reports of worsening traction of FEVR after treatment, a logical question is whether the worsening traction resulted from the treatment, or simply from the natural progression of disease in spite of treatment. Undoubtedly, some of the cases reported in the medical literature worsened as a result of severe disease that did not fully respond to available treatments. However, there is evidence that ablative treatments for PDR in the form of laser or cryotherapy, aimed at reducing neovascularization by eliminating the source of VEGF, can cause worsening of fibrous contraction after treatment. This phenomenon has been described as "crunch," and in addition to laser and cryotherapy, it has also been described after anti-VEGF treatments. Recently, the cytokines responsible for the changes seen clinically have been characterized and measured before and after treatment with laser and anti-VEGF in PDR.[46–48] Kuiper and associates[46] showed that the transition from neovascularization to fibrosis after

treatment with laser or anti-VEGF injections depended on the balance between levels of VEGF and connective tissue growth factor (CTGF). In their study, a shift in the balance between the pro-angiogenic VEGF and pro-fibrotic CTGF was associated with a switch from angiogenesis to fibrosis in PDR.[46] Instead of the term "crunch," these authors favor the term "angio-fibrotic switch" to describe the transformation to a more fibrotic and contractile state. Additional work by Van Geest and associates[47] confirmed that the CTGF/VEGF ratio is a strong predictor of vitreoretinal fibrosis in PDR and that anti-VEGF treatment causes increased fibrosis in PDR by shifting this ratio.[47] The timing of the angio-fibrotic switch in PDR was further defined in work by El-Sabagh and associates[48] to occur approximately 10 days after intravitreal anti-VEGF injections. A mechanism similar to that found in PDR may also be present in FEVR and may help explain the worsening identified in FEVR patients after treatment with laser ablation, cryotherapy, or anti-VEGF treatments.

During the period between the first description of FEVR in 1969 and the mid 1990s there was an evolution in the thinking about cryotherapy and laser treatment for FEVR. Early reports, including Benson's 1995 thesis,[10] describe treatment applied directly to abnormal vessels. In 1 example, Criswick and Schepens described photocoagulation "applied to retinal vessels proliferating temporally in both eyes," and in another case, "abnormal peripheral vessels" were "photocoagulated twice at one-month intervals."[1] In 1971, Gow and Oliver[2] described cryotherapy carried out with sufficient freezing "to incorporated the offending vessels in the iceball." Benson describes neovascularization being treated "directly with cryotherapy" in some cases, and in other cases, "the avascular zone" was treated with cryotherapy."[10] With the publication of results from the Cryo-ROP study in 1990, the idea of treating the avascular zone with cryotherapy or laser ablation became well established for ROP.[42] Because FEVR is phenotypically similar to ROP, it is logical that results of the Cryo-ROP trial would influence thinking about the technique of cryotherapy or laser ablation for FEVR. Benson's 1995 thesis is the first publication, of which these authors are aware, that specifically describes ablating peripheral avascular retina for FEVR.[10] Additionally, understanding of the role of VEGF in the pathogenesis of proliferative retinopathies evolved substantially in the years between the first descriptions of FEVR treatment and the publication of Benson's thesis in 1995.[10] Today there is an assumption that, if peripheral avascular retina is ablated, the drive toward neovascularization and fibrous proliferation will be reduced. This is certainly true for ROP. It is possible, however, that the pathogenesis of fibrous proliferation in FEVR is less dependent on VEGF derived from ischemia. In FEVR, there may be other mechanisms at work, perhaps related to abnormalities in Wnt signaling, that drive fibrous proliferation independently of the presence of ischemia. As such, worsening after treatment in FEVR may not only be related to the angio-fibrotic switch but also to limitations in the efficacy of ablating nonperfused peripheral retina.

Possible measures to reduce the risk of progression after laser may include supporting areas of traction with SB before laser. Other potential strategies may include staged laser treatments, as opposed to 1-time complete treatments, or pretreatment with serial anti-VEGF before laser. In addition, patients with predisposing clinical features to worsening traction after treatment, such as those with fibrous tissue in contact with the lens or subretinal yellow exudates, should be followed even more closely than usual with the expectation that prompt vitrectomy and/or SB may be necessary soon after laser. No clinical trial data currently exist to guide decisions regarding timing of treatment for FEVR. Some older reports emphasize the variable course of FEVR and, because some patients are stable for many years without treatment, recommend that treatment be applied only when there is high risk of worsening.[5,10] However, if treatment is delayed until there is evidence of "high risk," meaning the patient already has traction or exudation, the opportunity to apply treatment at a time that minimizes the risk of progression after treatment might have been missed. As a result, some investigators recommend a more aggressive approach.[17,24,31] Kashani and associates[17] recommend treating based on fluorescein agiographic leakage so that frank exudation can be prevented.[17] Present data suggest that treating before exudates are present would reduce the risk of worsening traction after treatment. It is important to note that the present findings, namely that some patients worsen with treatment, should not discourage timely laser ablation. On the contrary, a treatment paradigm consisting of laser ablation sooner rather than later in the disease process is supported by these data. In addition, when exudates or fibrous adhesions to the lens are present, prompt SB or PPV should be considered, either at the time of laser or shortly thereafter.

This study has several limitations. The first limitation is the relatively small number of patients available to analyze limits the ability to detect significant differences between baseline clinical features of those with and without worsening after treatment. The study is retrospective in nature, and follow-up was not complete at each time point. There are no adults in this series, and adults may have a lower risk of progression after treatment than children and adolescents.[5,6,10] Visual acuity data were not available for some patients due to examinations performed under anesthesia or because of the limited cooperation of children. Despite the limitations, this study provides useful data regarding the tendency for some FEVR patients to worsen after laser treatment and the baseline clinical features associated with worsening.

In summary, laser ablation of avascular retinas in patients with FEVR may result in worsening traction in a substantial proportion of patients. Patients and families should be counseled about this risk, and steps to reduce risk of progression should be considered. Potential measures to reduce risk will require further study to establish efficacy.

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