

# INTRAVITREAL RANIBIZUMAB TREATMENT FOR ADVANCED FAMILIAL EXUDATIVE VITREORETINOPATHY WITH HIGH VASCULAR ACTIVITY

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**Purpose:** To determine the efficacy of intravitreal ranibizumab (IVR) treatment for advanced familial exudative vitreoretinopathy with high vascular activity.

**Methods:** The retrospective interventional case series included 28 eyes (20 patients) that had IVR in combination or not with other treatment, for Stage 3 to 5 familial exudative vitreoretinopathy with active fibrovascular proliferation and prominent subretinal exudation. Outcome measures were fundus features after treatment, associated clinical variables, and genetic mutations.

**Results:** The age of patients at the first IVR ranged from 0.2 to 36 months. An average of 1.3 IVR injections per eye were given. Familial exudative vitreoretinopathy regressed in 16 (57%) eyes and progressed in 12 eyes (43%) after IVR. Laser and/or vitrectomy was performed on 13 eyes. The retina was reattached in 22 eyes (78%) after 24 to 58 months follow-up. Clinical variables associated with progression after IVR were preexisting fibrovascular proliferation over one quadrant and persistent vascular activity after the initial injection ( $P < 0.05$ ). Familial exudative vitreoretinopathy-causative genetic mutations in 11 patients were related to variable response to IVR treatment.

**Conclusion:** Intravitreal ranibizumab treatment may effectively regress advanced familial exudative vitreoretinopathy with high vascular activity in selected cases. Different treatment outcomes may be relevant to variable presentation and genetic heterogeneity of familial exudative vitreoretinopathy.

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**F**amilial exudative vitreoretinopathy (FEVR) is a hereditary vitreoretinal dystrophy with abnormal

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vasculogenesis and angiogenesis of the retina.<sup>1,2</sup> The disease can be inherited in autosomal dominant (AD), autosomal recessive, and X-lined recessive forms, with well-recognized genetic mutations affecting *NDP* (OMIM 300658), *FZD4* (OMIM 604579), *LRP5* (OMIM 603576), *TSPAN12* (OMIM 613138) in the Wnt signaling pathway, and *ZNF408* (OMIM 616465) and *KIF11* (OMIM 148760).<sup>3–7</sup> The clinical manifestations varied from attached retina (Stage 1–2 FEVR) with peripheral avascularity, straitening and branching of vessels, neovascularization, to the more advanced phenotypes of detached retina (Stage 3–5 FEVR) with extraretinal fibrovascular proliferation (FP), retinal exudates, and hemorrhages.<sup>8,9</sup> Specifically, retinal dragging or folds connecting to FP are representative phenotypes of advanced FEVR. Up to 20% of eyes with retinal folds related to FEVR may progress with increasing retinal detachment and blind-

ness due to activation of FP tissue that generates excessive retinal exudation and fibrosis formation.<sup>10,11</sup> High vascular activity in rapidly progressive FEVR has been linked to an upregulated level of vascular endothelial growth factor (VEGF) in ischemic retina with aberrant vasculature.<sup>12,13</sup>

The use of anti-VEGF agents in pediatric ocular disease has increased significantly over the past decade.<sup>14,15</sup> In cases with advanced FEVR, vascular activity was downregulated after intravitreal injection of anti-VEGF agents as adjunctive therapy to surgical repair or as an alternative once other interventions failed.<sup>13,15</sup> However, progression of the disease after anti-VEGF therapy in some cases with fibrotic traction raises a concern of the appropriateness of the therapy in different clinical scenarios.<sup>13,15</sup> Uncertainties exist in the course of evolution of advanced FEVR after different algorithms of anti-VEGF treatment in the candidates with varying clinical and genetic backgrounds.

Ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland, and Genentech, Inc, South San Francisco, CA) is one of the commonly used anti-VEGF agents to regress aberrant neovascularization in pediatric retinal diseases, including retinopathy of prematurity (ROP).<sup>16</sup> During the past years, we attempted intravitreal ranibizumab (IVR) combined with or without other treatment modalities in eyes with highly active Stage 3 to 5 FEVR. In this article, we reported the treatment outcomes and measured associated clinical and genetic characteristics in these cases.

## Materials and Methods

The retrospective interventional case study included 28 eyes of 20 patients who had Stage 3 to 5 FEVR and received IVR treatment in Xinhua Hospital, Medical School, Shanghai Jiao Tong University, Shanghai, China, between January 1, 2010, and February 28, 2018. The study was conducted in accordance with the tenets of the Declaration of Helsinki and retrospectively approved by the Ethics Committee of Xinhua Hospital. Informed consent to any treatment and off-label use of ranibizumab was obtained from the legal guardians of patients after a detailed explanation of possible complications.

### *Diagnosis and Patient Inclusion*

The clinical diagnostic criteria for FEVR were as follows: a positive family history that was supportive but not mandatory, peripheral retinal avascularity, nonperfusion, vitreoretinal traction, retinal exudation, or retinal neovascularization in at least one eye and

full-term or preterm birth with a disease tempo not consistent with ROP.<sup>8,9</sup> FEVR was classified into five stages according to Pendergast and Trese<sup>9</sup> as follows: particularly, Stage 3, extramacular retinal detachment without (3A) or with exudate or leakage (3B); Stage 4B, macula-involving subtotal detachment without (4A) or with exudate or leakage (4B); and Stage 5 represents total retinal detachment in an open funnel (5A) or closed funnel configuration (5B).

Inclusion criteria for the study were patients who had at least one IVR therapy for Stage 3 to 5 FEVR with high vascular activity and were followed for at least 24 months after first IVR treatment and for more than 6 months after their last treatment. Patients suspected of having other entities such as rhegmatogenous retinal detachment, ROP, persistent fetal vasculature, Coats disease, or ocular toxocariasis were excluded.

### *Intravitreal Ranibizumab Treatment*

Indications of IVR treatment were high vascular activity of FP, manifested as vascular dilation, neovascularization or hemorrhage, and retinal exudation already or potentially involving the posterior pole.<sup>13,17</sup> Reinjection was considered if vascular activity persisted with unresolved subretinal fluid 1 month after initial IVR or high vascular activity returned after initial regression. Intravitreal ranibizumab treatment was not considered if vascular activity was low with subretinal exudate in peripheral fundus or if retinal detachment prevented a safe entry for intravitreal injection.

The procedures for IVR injection were performed under topical anesthesia. Intravitreal ranibizumab at 0.25 mg/0.025 mL (the same as that previously applied in Type 1 ROP) was injected with a 30-gauge needle penetrating at the age-adjusted site posterior to the limbus through pars plicata or plana where there was no anteriorly dragged retina.<sup>16</sup> Follow-up was tailored to the response to the treatment, at Days 3 and 7 after IVR treatment and then biweekly, monthly, bimonthly, and then once in half a year.

### *Combined Laser or Vitrectomy*

A laser under indirect ophthalmoscope (LIO) was applied to leaking vessels and avascularity on the attached retina. Lens-sparing vitrectomy was indicated for localized vitreoretinal traction affecting the posterior pole. Endolaser photocoagulation to attached avascular retina was performed during vitrectomy where possible. Vitrectomy combined with lensectomy through limbal incisions was performed to treat contraction of retrolental fibrosis from the elevated

retina. Postoperative follow-up was regular at an interval of 1 to 3 months.

### Genetic Testing

DNA samples were extracted from peripheral blood from probands and their direct family members. Variants of the *NDP*, *FZD4*, *LRP5*, *TSPAN12*, *ZNF408*, and *KIF11* were screened using a targeted gene capture and next generation sequencing method (MyGenostics, Baltimore, MD).<sup>18,19</sup> A novel variant was reported if 1) it was with low minor allele frequency (less than 0.001) against 1,000 genomes database and 2) it was predicted to be conserved in silico analysis by GERP++, as well as damaging or disease causing at least by one of three algorithms (PolyPhen-2, Sorting Intolerant From Tolerant, and Mutation Taster), or it was predicted to be nonconserved by GERP++ but damaging or disease causing in at least two of the three algorithms. Sanger sequencing of family members validated identified variants. Each in silico-predicted novel variant was assessed for genotype-phenotype cosegregation in the affected families.

### Outcome Measures and Statistics

The main outcome measures were response to IVR and final retinal status. Response was categorized as follows: 1) progression, the development to a higher stage of FEVR, or worsening retinal detachment, with persistent vascular activity and/or prominent vitreoretinal traction by fibrosis or 2) regression, defined as decreased vascular activity and reduced retinal detachment. Final retinal status was categorized as follows: 1) reattached retina, when the retinal folding was dry with resolution of retinal exudation; 2) partly reattached retina, with reattached posterior retina; or 3) detached retina, with the posterior retina or the total retina detached. Data collection included demographic and ophthalmic data, genotypes, fundoscopic findings by indirect ophthalmoscope under scleral indentation, fundus imaging or fluorescein angiography by RetCam (Clarity Medical Systems, Pleasanton, CA) or Optos (PLC; Dunfermline, Scotland, United Kingdom), intraocular pressure, ultrasound A-scan and B-scan, ultrasound biomicroscopy, procedure(s) performed, and length of follow-up. The extent of preexisting FP tissue and retinal detachment was recorded. In the presence of obscured media, the extent of FP and retinal detachment was determined by fundoscopic findings along with examinations on B-scan and ultrasound biomicroscopy.

Statistical analysis was performed with version 22.0 of SPSS software (SPSS, Inc, Chicago, IL). Data were

compared using the Student *t*-test, Mann-Whitney *U* test, or Fisher exact test according to the type of variables.

## Results

### Baseline Characteristics

Fourteen boys and 6 girls at an age from 0.2 to 36 months were included (Table 1). There were 24 eyes (85%) with Stage 3B or 4B FEVR and 4 eyes (15%) with Stage 5A FEVR with shallow retinal detachment, all showing retinal dragging or folding to peripheral FP tissues. Five eyes received FA to estimate vascular leakage after IVR. The median follow-up time from the initial IVR was 24.5 months.

### Response to Intravitreal Ranibizumab Treatment

An average of 1.3 injections of ranibizumab were given to 28 eyes (Table 2, Figures 1 and 2). After the initial IVR treatment, 20 (71%) of the 28 eyes showed reduced retinal vascular activity. Eight eyes (29%) showed persistence, and one of four retreated eyes attained a reduction of vascular activity. Four eyes (14%) showed recurrent vascular activity 11 to 20 months after the initial IVR and had decreased vascular activity after reinjection. Totally, 15 eyes receiving primary IVR treatment and one eye receiving concurrent IVR and LIO (16 eyes, 57% of the 28 eyes)

Table 1. Demographics of Patients With Advanced FEVR Receiving IVR Treatment

Variables	N (%)
Patients, n	20
Median age at the first IVR injection, months (range)	8 (0.2–36)
Sex, n (%)	
Male	14 (70)
Female	6 (30)
Family history, n (%)	
Yes	14 (70)
No	6 (30)
Median follow-up time since first IVR injection, months (range)	24.5 (24–58)
Eye included, n (%)	28 (100)
Bilateral	16 (40)
Unilateral	12 (60)
Staging of fundus, n (%)	
3B	1 (3)
4B	23 (82)
5A	4 (15)
Fellow eye not included, n	12
Staging, n (%)	
1–2	5 (42)
3–5	7 (58)

Table 2. Intravitreal Ranibizumab Treatment Response in Eyes With Advanced FEVR

Variables	Regression After IVR	Progression After IVR	<i>P</i>
<b>Baseline</b>			
Distribution of staging, n (%)			0.597*
3B	0	1 (8)	
4B	14 (88)	9 (75)	
5A	2 (12)	2 (17)	
FP > 1 quadrant, n (%)	2 (13)	8 (67)	0.004*
RD > 1, n (%) quadrant	5 (31)	8 (67)	0.063*
Retinal hemorrhage, n (%)	7 (5)	4 (33)	0.705*
<b>Treatment pattern</b>			
Primary IVR, n (%)	15 (94)	10 (83)	0.560*
Sequential IVR after LIO or concurrent IVR and LIO, n (%)	1 (6)	2 (17)	
IVR repetition, n (%)	3 (19)	5 (41)	0.231*
Mono-IVR, n (%)	13 (81)	11 (59)	
<b>Vascular activity, n (%)</b>			
Reduction after first IVR, n (%)	15 (94)	5 (42)	
Persistence after first IVR, n (%)	1 (6)	7 (58)	0.004*
IVR repetition, n	1	3	
Reduction after second IVR, n	1	0	
Recurrence after first IVR, n (%)	3 (19)	1 (8)	0.613*
Median time to first IVR, months (range)	14 (11–20)		
IVR repetition, n	2	2	
Reduction after second IVR, n	2	2	
Resolution of retinal exudation, median time to first IVR, months (range)	9.5 (1–19)		
Organization and fibrosis after first IVR, n (%)	16 (100)	12 (100)	0.664*
Median time to first IVR, months (range)	3.0 (1–10)	3.0 (1–12)	0.698†
Median follow-up time to first IVR for eyes (range, months)	24 (24–58)	25 (24–44)	0.250†
<b>Total, n</b>	<b>16</b>	<b>12</b>	

\*Fisher exact test.

†Mann–Whitney *U* test.

RD, retinal detachment.

showed regression of FEVR. Retinal exudates resolved at a median time of 9.5 months after the initial IVR.

The 28 eyes developed organization and fibrosis around the FP and retinal folds at a median time of 3 months after the initial IVR. As a result, 10 eyes

receiving primary IVR treatment and 2 eyes receiving concurrent or sequential IVR and LIO (12 eyes, 43% of the 28 eyes) progressed. Five eyes showed localized vitreoretinal contraction around FP inducing retinal elevation, and two of the five eyes developed a shallow anterior chamber and secondary glaucoma.



**Fig. 1.** Representative fundoscopic photographs demonstrating regression of FEVR after primary IVR therapy. **A.** Right eye with Stage 4B FEVR of a 4-month-old girl (Patient 4 in Table 4) showed prominent subretinal exudation, retinal hemorrhage, and active FP extending smaller than one quadrant (by RetCam Imaging

System); **(B)** regression of FEVR with absorbed subretinal exudation 6 months after initial IVR injection. New fibrosis formation was wrapping the preexisting FP tissue and the retinal folds; **(C)** reattached retina with dry folds was observed 58 months after IVR (by ultra-wide-field scanning laser ophthalmoscopy).

The other 7 eyes progressed to a higher stage of disease with persistent vascular activity and extensive fibrous membrane formation, and 3 eyes with Stage 5B FEVR developed a flat anterior chamber.

#### Further Interventions and Final Outcomes

Three of the 16 eyes with regression after IVR received LIO (Table 3 and Figure 2). Eight of the 12 eyes with progression after IVR received vitrectomy combined with or without lensectomy and 6 eyes achieved retinal reattachment. Two eyes with secondary glaucoma attained normal intraocular pressure postoperatively.

Twenty-two (78%) of 28 eyes achieved a final reattached or partly reattached retina with reduced vascular activity and 6 eyes (22%) showed active FEVR with a detached retina. In the treatment algorithm, retinal reattachment was attained in 12 (43%) of the 28 eyes receiving mono-IVR treatment and in 10 (36%) eyes receiving combined management.

#### Characteristics Associated with Treatment Outcomes

Relating to clinical variables, preexisting FP over one quadrant and persistent vascular activity after the initial IVR were more frequently observed in eyes showing progression after IVR treatment compared with those showing regression (67% vs. 13%,  $P = 0.005$ ; 58% vs. 6%,  $P = 0.004$ ) (Tables 2–4). In addition, preexisting FP or retinal detachment over one quadrant was observed more frequently in eyes finally

attaining retinal reattachment compared with those without retinal reattachment (100% vs. 40%,  $P = 0.001$ ; 100% vs. 32%,  $P = 0.005$ ).

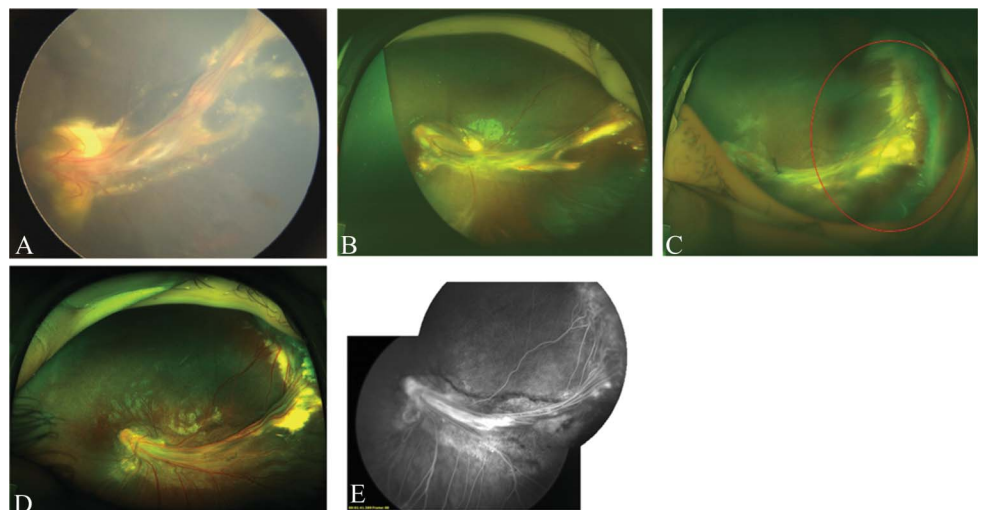
#### Genotypes

Genotyping among 15 patients revealed 6 previously reported variants and 5 novel variants (Table 4 and see Table 1, Supplemental Digital Content 1, <http://links.lww.com/IAE/B396>).<sup>5,19–22</sup> Two patients harboring hemizygotous missense of *NDP* were diagnosed with XR FEVR, and Norrie disease was excluded in the absence of mental retardation and hearing loss. The three treated eyes of the two patients showed regression of disease after IVR and achieved final retinal reattachment. Nine patients showed AD FEVR. Nine patients harboring heterozygous mutations had AD FEVR. The number (occurrence of regression: progression) of eyes for each heterozygous gene variant was 3:1 for *FZD4*, 2:4 for *LRP5*, 0:1 for *KIF11*, and 0:1 for *TSPAN12*. Meanwhile, the number of eyes with progression for each heterozygous gene (missense: null mutation including frameshift and nonsense) was 0:1 for *FZD4*, 3:1 for *LRP5*, 0:1 for *KIF11*, and 1:0 for *TSPAN12*. Moreover, all bilateral cases with mutations (Patient 13, 14, 18, and 19) showed regression in one eye and progression in the other eye after IVR treatment (Table 4).

#### Discussion

In a substantial number of eyes with advanced FEVR, active FP on retinal folds and vitreous

**Fig. 2.** Fundoscopic and fluorescence angiography photographs of progression of FEVR after IVR therapy and further lens-sparing vitrectomy. **A.** RetCam Imaging System revealed prominent subretinal exudation and active FP (<one quadrant) in the left eye with Stage 4B FEVR in a 30-month-old boy (Patient 9 in Table 4). There was organization of subretinal exudates and preretinal fibrous membrane. A missense mutation in *LRP5* was identified. **B.** Reduced subretinal fluid and increased fibrous membrane along the tapering retinal folds 10 months after initial IVR injection (by ultra-wide-field scanning laser ophthalmoscope). **C.** New fibrous membrane



around FP and recurrent subretinal fluid (red ring) induced progression of FEVR 20 months after the initial IVR injection. Lens-sparing vitrectomy combined with another IVR was performed to treat recurrent vascular activity and preretinal membrane. **D.** Ultra-wide-field scanning laser ophthalmoscope 1 month after surgery revealed reattached posterior retina and residual subretinal exudates in periphery; **(E)** fluorescence angiography by RetCam Imaging System 2 months after surgery showed regressed FP tissue and partly reattached retina.

hemorrhages were observed, and prominent subretinal fluid hampered an effective access by laser, cryotherapy, and scleral buckling.<sup>8,17,23</sup> In particular, active FP was accompanied with a strong vascular component in patients with FEVR younger than 36 months for whom vitrectomy may risk excessive inflammation and recurrent proliferation.<sup>8,17,23,24</sup> The current study included a case series of young patients with Stage 3 to 5 FEVR who were treated by IVR in combination or not with other modalities. The treatment patterns, relevant efficacy, and complications in cases with varying fundus features and genetic backgrounds provide important clinical implications.

The study highlighted the effectiveness of primary IVR treatment in regressing advanced FEVR and resolving retinal exudates in more than half of the eyes. The regression rate was comparable with that in the literature observing stabilization of Stage 3 or worse FEVR in approximately 50% eyes after adjunctive anti-VEGF treatment or sequential anti-VEGF treatment following other treatment.<sup>13,15</sup> Resolution of subretinal fluid took months after primary IVR treat-

ment, accompanied with reduced vascular permeability and proliferation of FP.<sup>12</sup> Vascular activity recurred in a minority of eyes at an interval of almost 1 year after IVR, which is longer than the recurrence time around 2 months after IVR treatment in eyes with Type 1 ROP.<sup>16</sup> Thus, reinjection was not as frequent as in a case series with active FEVR undergoing 3.5 IVB treatments per eye.<sup>15</sup>

Persistent vascular activity and fibrotic contraction of FP drove progression of FEVR after IVR in 43% eyes. The rate was similar with about 50% progression in eyes receiving adjunctive bevacizumab in surgery or after alternative pegaptanib sodium after laser or intravitreal triamcinolone acetonide injection.<sup>13,15</sup> On one hand, persistent vascular activity of FP occurred in nearly one-third treated eyes and did not respond well to reinjection. On the other hand, organization and fibrosis proliferated prevalently along FP and retinal folds in eyes with FEVR after anti-VEGF therapy. The cicatricial change may last for months within the natural course of FEVR-related retinal folds, and it also may be an adverse effect induced by imbalance of cytokines after anti-VEGF blockade.<sup>10,11,25</sup> The cicatricial change around FP may limit vascular leakage but risk retinal dragging and bulging of the iris-lens diaphragm. The characteristics of cicatrices in advanced FEVR are dissimilar with that in Type 1 ROP after anti-VEGF therapy. The latter displays circumferential contraction of fibrovascular ridges or pre-papillary fibrosis mostly within 1 month.<sup>25</sup> Thus, closely monitoring the FP in retinal folds is essential in managing eyes with advanced FEVR. In this study, concurrent or previous LIO did not significantly improve the response to IVR, possibly due to its incompetence to the detached retina.

Monotherapy by IVR or combined treatment in this case series resulted in a 78% retinal reattachment rate, almost identical to 40% to 88% in eyes undergoing vitrectomy for Stage 3 or worse FEVR in several cohorts.<sup>8,17,23,24</sup> The data confirmed the efficacy of mono-IVR treatment not only in resolving retinal exudation in eyes with advanced FEVR during postoperative months but also in possibly postponing further interventions. Further interventions after primary IVR, such as laser or vitrectomy in a less active status may stabilize FEVR disease and improve retinal structure. In eyes showing progression, timely surgical strategies may be beneficial for localized or extensive proliferation once reduced vascular activity is transiently reduced after anti-VEGF treatment.

Eyes with progression after IVR treatment or final retinal detachment may be associated with characteristics including preexisting FP or retinal detachment over one quadrant, and postinjection persistence of

Table 3. Final Anatomical Outcomes in Eyes With Advanced FEVR

Variables	Retinal Reattachment (%)	Retinal Detachment (%)	P
Baseline			
Distribution of staging, n (%)			0.050*
3B	0	1 (17)	
4B	20 (91)	3 (50)	
5A	2 (9)	2 (33)	
FP > 1 quadrant, n (%)	4 (40)	6 (100)	0.001*
RD > 1, n (%) quadrant	7 (32)	6 (100)	0.005*
Retinal hemorrhage, n (%)	10 (45)	1 (17)	0.355*
Treatment pattern			
Mono-IVR, n (%)	12 (55)	3 (50)	1.000*
Combined treatment, n (%)	10 (45)	3 (50)	
LIO, n	5	1	
LSV or L + V, n	6	2	
Lens status			
Phakia, n (%)	19 (86)	4 (67)	
Aphakia	3 (14)	2 (33)	
N	22	6	

\*Fisher exact test.  
Mann-Whitney U test.  
LSV, lens-sparing vitrectomy; L + V, lensectomy + vitrectomy; RD, retinal detachment.

Table 4. List of Patients and Included Eyes Receiving IVR Treatment for Advanced FEVR

Pt	Sex	First IVR, Months	Gene Name	Variants (Protein)	Effect	Inheritance/ Allele Status	Eye	Stage	IVR Treatment (Time Interval)	Response to IVR	Further Treatment (Time since First IVR)	Final Anatomical Outcome
1	M	19	NDP	c.118A>G (p.M40V) <sup>20</sup>	Missense	XL/hemi	OD	5A	1 IVR	Regression		Reattached
2	F	6	KIF11	c.2524C>T (p.Q842X) <sup>19</sup>	Nonsense mutation	AD/het	OS	4B	1 IVR (Previous LIO 3 months before IVR)	Progression to 5A	L+V (3 months after IVR)	Reattached
3	M	1	NDP	c.17T> C (p.L6P)†	Missense	XL/hemi	OD	4B	1 IVR	Regression	LIO (9 months)	Reattached
4	F	4	No testing	NA	NA	/	OS	4B	1 IVR	Regression	LIO (11 months)	Reattached
5	F	9	Negative	NA	NA		OS	4B	1 IVR	Regression with new fibrosis	LSV (12 months)	Reattached
6	F	36	FZD4	c.227delA (p.E76Gfs*4) <sup>21</sup>	Frameshift	AD/het	OD	4B	1 IVR	Regression		Reattached
7	M	13	Negative	NA	NA		OD	5A	1 IVR	Progression to 5B	L + V (3 months)	Unfolded
8	M	8	No testing	NA	NA		OS	4B	1 IVR	Progression with new fibrosis	LSV+ endolaser (3 months)	Reattached
9	M	30	LRP5	c.3892T>C (p.C1298R)†	Missense	AD/het	OS	4B	1 IVR	Progression	LSV + second IVR (20 months)	Partly reattached
10	F	8	No testing	NA	NA		OD	4B	2 IVR (1 month)	Regression, cataract		Reattached
							OS	4B	2 IVR (1 month)	Progression to 5A		Detached
11	F	2	Negative	NA	NA		OS	4B	1 IVR	Regression		Reattached
12	M	19	No testing	NA	NA		OD	4B	1 IVR	Regression		Reattached
13	M	10	LRP5	c.4178dup T(p.I1394Hfs*156)†	Frameshift	AD/het	OD	5A	2 IVR (3 months)	Progression		Detached
14	M	3	TSPAN12	c.300G> C (p.L100F)†	Missense	AD/het	OS	4B	1 IVR	Regression		Reattached
							OD	4B	1 IVR	Progression to 5B	L + V (14 months)	Unfolded
							OS	4B	1 IVR	Regression		Reattached
15	M	8	Negative	NA	NA		OD	4B	1 IVR	Regression	LIO (11 months)	Reattached
16	M	7	LRP5	c.1264G>A(p.A422T) <sup>22</sup>	Missense	AD/het	OD	3B	2 IVR (12 mons)	Increased hemorrhage, progression to 4B		Partly detached with vascular activity

Table 4. (Continued)

Pt	Sex	First IVR, Months	Gene Name	Variants (Protein)	Effect	Inheritance/ Allele Status	Eye	Stage	IVR Treatment (Time Interval)	Response to IVR	Further Treatment (Time since First IVR)	Final Anatomical Outcome
17	M	12	FZD4	c.347C>T (p.P116L)†	Missense	AD/het	OD	5A	2 IVR (11 mons)	Regression		Partly reattached
18	M	3	FZD4	c.1282_1285del (p.D428Sf s*1) <sup>5</sup>	Frameshift	AD/het	OD	4B	2 IVR (14 months)	Progression, shallow anterior chamber with increased IOP	L + V + endolaser (18 months)	Reattached
19	M	3.5	LRP5	c.1676A>G(p.Y559C)†	Missense	AD/het	OS	4B	2 IVR (14 mons)	Regression		Reattached
							OD	4B	1 IVR+ LIO	Regression		
							OS	4B	1 IVR+ LIO	Progression to 5A		
20	M	0.2	No testing	NA	NA		OD	4B	1 IVR	Progression, shallowing chamber, increased IOP	L + V + endolaser (8 months)	Reattached, normal IOP
							OS	4B	1 IVR	Regression		Reattached

†Novel mutations.

IOP, intraocular pressure; L, lensectomy; LSV, lens-sparing vitrectomy; V, vitrectomy.



vascular activity. These variables may indicate the severity of vascular anomalies and aggressive behavior of FEVR disease. A large extent of active FP is more likely to show persistent vascular activity after anti-VEGF and attract extensive fibrosis formation during the cicatricial stage. Extensive retinal detachment may imply high vascular activity, the long period of the disease, and the poor function of the retinal pigment epithelium cells. Thus, we recommend that IVR therapy should be used with extreme caution in eyes with these severe manifestations and that a vitrectomy to rescue complications in the cicatricial stage be planned.

Response to IVR treatment may be relevant to the characteristics of mutations of FEVR-causative genes but highly variable. Reportedly, there may be more chance that selected cases showing XR FEVR related to a single-point mutation of *NDP* take a less aggressive course than those with severe Norrie disease due to deletions and truncations.<sup>18,20,26</sup> Thus, it is conceivable that patients with XR FEVR due to missense in *NDP* showed a relatively good response to IVR therapy in this case series.<sup>4</sup> Autosomal dominant FEVR related to *FZD4*, *LRP5*, *TSPAN12*, and *KIF11* in the series showed varying severity and responded diversely to IVR treatment among individuals and eyes. For instance, the patient harboring a “hotspot” frameshift mutation (c.1282\_1285del)<sup>5</sup> of *FZD4* showed bilateral retinal folds that responded differently to IVR, whereas another frameshift and a missense in *FZD4* were associated with a good response to IVR treatment. Reportedly, missense (c.1264G>A) of *LRP5* may induce AD FEVR in young probands with severe retinal detachment.<sup>22,25</sup> The patient carrying the variant responded poorly to IVR treatment and had final retinal detachment. However, another missense and a frameshift in *LRP5* were detected in patients showing different outcomes in bilateral eyes. Thus, a genotype–phenotype correlation could not be made from the limited cases.

The study is limited in its inherent retrospective nature, lack of a control arm, limited cases for genotype–phenotype correlation and statistical analysis, and a relatively short-term follow-up period for the life-long progressive disease. The case series may be biased toward the phenotype of FEVR with prominent subretinal exudates that was more likely to indicate an IVR therapy before other interventions. The lack of a control arm of other management methods or anti-VEGF agents in different dosages may limit the assessment of the application of the treatment.

In conclusion, IVR therapy may be effective in reducing vascular activity in selected patients with advanced FEVR. Primary usage is valuable to regress exudative retinal detachment in advanced FEVR but not for fibrotic traction. Different treatment outcomes may be relevant to variable expressivity and genetic heterogeneity of FEVR. A well-planned algorithm of anti-VEGF monitoring may be safer and more effective in preventing progression of eyes with advanced and vascularly active FEVR.

**Key words:** familial exudative vitreoretinopathy, ranibizumab, retinal fold, gene.

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