• Clinical Research •

The role of intravitreal ranubizumab in the treatment of familial exudative vitreoretinopathy of stage 2 or greater

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Abstract

• AIM: To evaluate the role of intravitreal ranubizumab (IVR) in the treatment of familial exudative vitreoretinopathy (FEVR) of stage 2 or greater either as primary or an ajunct to conventional treatments.

• METHODS: Retrospective, non-controlled clinical study. Thirty patients (37 eyes) diagnosed with FEVR were enrolled. Twenty patients (66.67%) were male and 10 patients (33.33%) were female. Age ranged from 0.4 to 35 years old (median 3y). IVR was used either as primary or as a combined therapy according to the retinal neovasuclar activities. The follow up ranged from 1 to 57mo with mean 16.73±15.73 (median 11)mo. The treatment effect of retinal neovasuclar activites were recorded as well as the ocular and systemic side effects.

• RESULTS: Among 30 patients (37 eyes), 10 eyes received single IVR, 1 eye received 2 injections. Three eyes were treated with IVR and simutanous laser photocoagulation. Laser indirect ophthalmoscopy (LIO) was applied in 5 eyes 1mo after the primary IVR. Seven eyes were treated surgically following the primary IVR due to persistent retinal neovasuclar activities and retinal traction. IVR was used as combined treatment with vitrectomy in 11 eyes. Retinal neovascular regression was notified 1mo following the primary IVR in all eyes. Neither systemic nor ocular complications were recorded.

• CONCLUSION: IVR may be an effective modality in the treatment of FEVR either as primary or as an ajunct to the conventional therapies. The long term effect and safty of IVR still need further research.

• **KEYWORDS:** familial exudative vitreoretinopathy; anti-vascular endothelial growth factor; treatment

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INTRODUCTION

Familial exudative vitreoretinopathy (FEVR) was first discribed by Criswick and Schepens[1] in 1969 as a genetically related retinal vasuclar malformation, characterized by peripheral retinal vasucular abnormalities including retinal avascular zone, retinal neovascularization, exudate, macular traction, traction or rhegmatogenous retinal detachment (RD)[2-3]. The clinical features were confirmed by Canny and Oliver[4] in 1976 with fundus fluorescein angiography.

Although FEVR is known as familial, the presence among family members remains variant. Patients with FEVR can be asypomatic with peripheral avascular zone or vision loss as a result of retinal detachment if left untreated. Reports indicated that Wnt-receptor/β-catenin pathway was related with retinal formation and regulations of vascular endothelial growth factor (VEGF) expression. Mutation of protein that modulates the pathway might be involed in the pathogenesis of FEVR[5-7]. Anti-VEGF therapy was tried for FEVR in a few reports and was found to be effective[8-10]. Lucentis (Ranubizumab, Novatis Company) was used in our study for inhibation of retinal neovascular activities as primary or combined therapy in FEVR of stage 2 or greater.

SUBJECTS AND METHODS

Retrospective, non-controlled clinical study. The study protocol was reviewed and approved by the Ethnic Committee of the First Affiliated Hospital of Chongqing Medical University and Beijing Tongren Hospital. Thirty patients (37 eyes) diagnosed with FEVR of stage 2 to 5 were enrolled in our study. Twenty patients (66.67%) were male and 10 patients (33.33%) were female. Age ranged from 0.4 to 35 years old (median 3y). Intravitreal ranubizumab (IVR) was used either as primary or as a combined therapy according to the retinal neovasuclar activities. The follow up ranged from 1 to 57mo with mean

16.73±15.73 (median 11)mo. The treatment effect of retinal neovasuclar activites were recorded as well as the ocular and systemic side effects. Patients were evaluated with ocular check-up including visual acuity (VA), intraocular pressure, indirect ophthalmoscopy, slit lamp examination, retinal photography and fundus fluorescein angiography. There were 16 patients old enough to cooperate with VA examination, the rest of patients were too young to VA taking. Their visions were discribed by parents according to their visual behaviors. Staging was done in accordence with the following classification (Pendergast and Trese, 1998):

Stage 1, avascular retina without extraretinal vessels; Stage 2, avascular retina with extraretinal vessels (A, no exudate; B, with exudate); Stage 3, partial RD-fovea spared (A, no exudate; B, with exudate); Stage 4, partial RD-fovea involved (A, no exudate; B, with exudate); Stage 5, total RD (A, no exudate; B, with exudate).

All patients diagnosed with FEVR of stage 2 or greater received intravitreal injection of ranubizumab. Consent form was signed prior to the treatment. Retinal photocoagulation was performed in cases with persistent or recurrent neovasuclar activities like hemorrahge and exudate. Buckle surgery was done when tractional RD detected.

Intravitreal injection of ranubizumab was performed 2-3 mm away from limbus. Dosage of injection was 0.5 mg (0.05 mL) ranubizumab for adult patient and 0.25 mg (0.025 mL) for children (age below 18 years old). All patients were examined on the following day and 1mo after injection, then followed monthly to determine if the vascular changes were stable or further treatments needed.

RESULTS

The enrolled patients' data at baseline was listed in Table 1. Among 30 patients (37 eyes), 10 eyes received single IVR, 1 eye received 2 injections. Three eyes were treated with IVR and simutanous laser photocoagulation. Laser indirect ophthalmoscopy (LIO) was applied in 5 eyes 1mo after the primary IVR. Seven eyes were treated surgically following the primary IVR due to persistent retinal neovasuclar activities and retinal traction either with vitrectomy or buckle surgery (Figures 1-3).

IVR was used as combined treatment with vitrectomy in 11 eyes. In eyes underwent vitrectomy, vitreous hemorrhage and traction were the main reasons for surgical intervention. IVR facilitied the retinal neovascular regression which minimize the chances of surgical complications such as bleeding and itraogenic retinal breaks.

Retinal neovascular regression such as diminished retinal hemorrhage and exudation was notified at 1mo following the primary IVR in all eyes, which was determined with indirect ophthalmoscopy, fundus photogaphy and fundus fluorescein angiography. Vision in all patients improved or remained stable except in one patient with visions in both eyes decreased from 0.05 to light perception and no light perception due to persistent tractional RD. No IVR related ocular and systemic complications were recorded during follow up. The details of treatment and follow up were listed in Table 2.

Table 1 Patients' data at baseline *n* (%)

Variable	Data
Sex (*n*=30), 37 eyes	
M	20 (66.67)
F	10 (33.33)
Mean age (range)	6.2±8.31(0.4-35)y
≤1y	7 (23.3)
1-3y	9 (30)
3-10y	9 (30)
>10y	5 (16.67)
Stages (*n*=37)	
Stage 2	
2A	4 (10.86)
2B	16 (43.24)
Stage 3	
3A	4 (10.81)
3B	3 (8.11)
Stage 4	
4A	5 (13.51)
4B	4 (10.81)
Stage 5	
5B	1 (2.70)

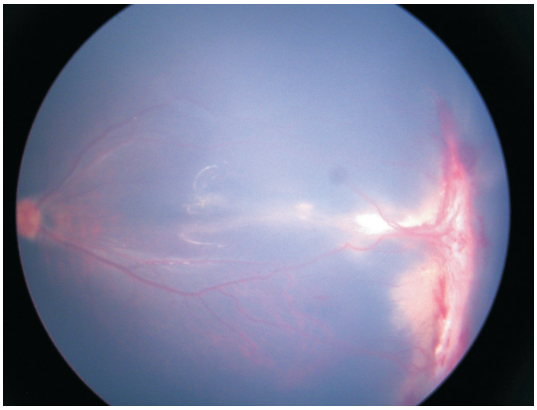

Figure 1 Fundus image of patient No.4 before IVR, showing retinal hemorrhage, exudate and minimal peripheral traction retinal detachment.

DISCUSSION

For patients with FEVR, the main causes of vision loss are retinal neovascularization and the associated complications, such as traction RD and macular edema *etc*. The treatment target of FEVR of stage 2 or greater is to minimize the retinal neovascular activities by all possible means. Conventional therapies include laser photocoagulation, cryotherapy, or buckle and vitrectomy in cases with RD.

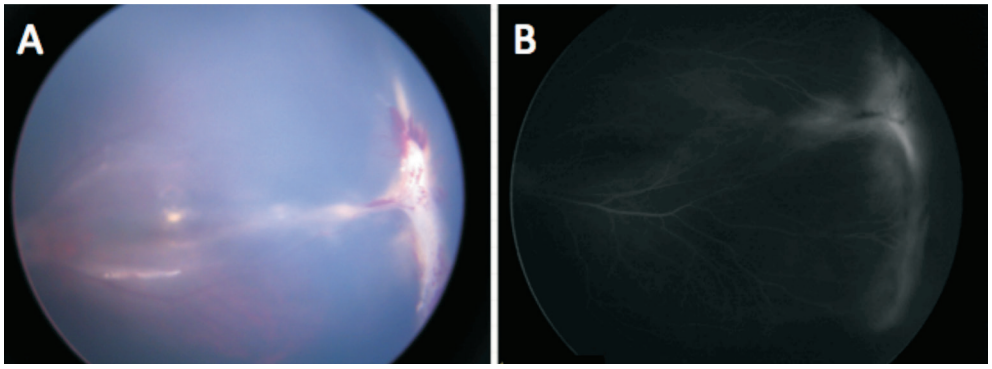

Figure 2 Fundus photographs of patient 1mo after IVR Color image (A) and fluorescence fundus angiography (B) of patient No.4 showing reduced retinal hemorrhage, exudate and leakage.

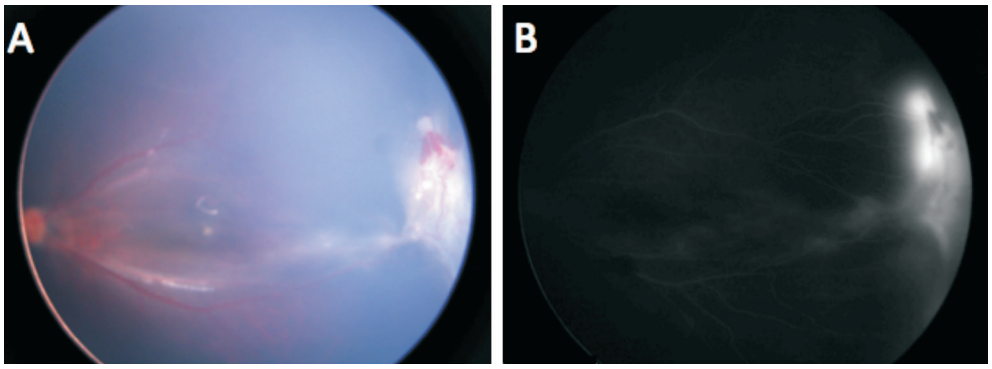

Figure 3 Fundus photographs of patient 4mo after IVR Images of fundus (A) and fluorescence fundus angiography (B) of patient No.4 showing retinal hemorrhage and exudate remained minimal, traction retinal detachment increased. The patient received buckle surgery afterwards and remained stable.

Anti-VEGF therapy has become the primary treatment of retinal neovascular problems such as wet age-related macular degeneration (AMD), retinal vein occlusion and diabetic macular edema. It has been found to be able to reduce retinal vascular permeability and reduction of exudate. There have been a number of reports of anti-VEGF for pediatric retinal diseases like Coat's disease and retinopathy of prematurity[11-20]. Reports indicated that Wnt-receptor/β-catenin pathway was related with retinal formation and regulations of VEGF expression. Mutation of protein that modulates the pathway might be involed in the pathogenesis of FEVR[5-7]. Anti-VEGF therapy was tried for FEVR in a few reports and was found to be effective[8-10].

In our study, the IVR was used as a primary or combined treatment of FEVR in case of stage 2 and greater, in which retinal neovascular activities were present. Conventional laser photocoagulation reacts poorly in severe retinal hemorrhage and exudate while cryotherapy causes prominent intraocular inflammation. The primary anti-VEGF therapy helped to reduce the retinal hemorrhage and exudate, which greatly facilitated the photocoagulation effect with minimal intensity. In our study, retinal neovascularization was significantly diminished following IVR with the reduction of hemorrhage and exudate in all patients. Secondary laser photocoagulation was applied in 5 eyes because of persistent precence of neovascular activities. Two eyes was finally treated with buckle surgery because of increased traction. IVR was used as combined treatment with vitrectomy in 11 eyes. In eyes underwent vitrectomy, vitreous hemorrhage and traction were the main reasons for surgical intervention. IVR facilitied the retinal neovascular regression which minimize the chances of surgical complications such as bleeding and itraogenic retinal breaks.

Vision in the most of the eyes with IVR had remained stable or improved in our study. Similar effect of anti-VEGF for FEVR was reported by Quiram *et al*[8].

Complications of IVR may include vitreous hemorrhage, retinal breaks and detachment, endothphalmitis and uncertain systemic side effects. In our study, neither ocular nor systemic side effects were recorded, implying that IVR for FEVR may be a safe treatment as recongnized in wet AMD treatment.

In general, our study has shown that IVR may be an effective modality in the treatment of FEVR either as the primary or as an ajunct to the conventional therapies. The long term effect and safty of IVR still need further research.

Table 2 Eyes underwent IVR for FEVR of more than stage 2

No. (*n*=30)	Sex	Age at baseline (y)	Eye	Stage at initial therapy	With VH	Initial therapy	Followed therapy (Stage) (Interval months)	Preoperative VA	VA at last follow up	Follow up (mo)
1	F	0.4	OD	2B		IVR	LIO (2B)(1)			5
			OS	2B		IVR	LIO (2B)(1)			2
2	M	4	OD	2B		IVR				4
			OS	2B		IVR				3
3	M	3	OD	2B		IVR				4
4	F	8	OD	4B	+	IVR		0.02	0.08	12
5	F	31	OD	2B		IVR		1	1	8
			OS	2B		IVR		1	1	8
6	M	2	OD	2B		IVR	IVR (2A)(1)			3
7	M	35	OD	2B		IVR	LIO (2B)(1)	1	0.8	11
			OS	2B		IVR	LIO (2B)(1)	1	1	11
8	M	3	OS	2B		IVR				12
9	M	0.3	OD	2B		IVR	LIO (2B)(1)			7
10	M	9	OD	2B		IVR	LSV+PC+IVR+C2F6 (3A)(24)		0.5	42
11	M	0.3	OD	4A		L&V+PC+IVR				1
12	F	6	OS	4B	+	IVR		LP	LP	6
13	M	2	OS	2B		IVR				13
14	F	1	OD	2A		IVR+LIO				6
		1	OS	2A		IVR+LIO				6
15	F	14	OD	4A	+	LSV+PC+IVR		0.2	0.2	10
16	F	5	OS	5A	+	L&V+PC+IVR+SO		HM	HM	20
17	F	4	OD	3B		IVR[a]	L&V+PC+IVR (3B) (7)		0.3	21
18	M	0.92	OD	4B		L&V+PC+IVR				23
			OS	4B		L&V+PC+IVR				23
19	M	2	OS	4B		LSV+PC+IVR			0.3	24
20	M	3	OD	4A	+	LSV+PC+IVR			CF	49
21	M	0.67	OS	3A	+	IVR	LSV+PC+IVR (3B)(0.25)			40
22	M	4	OS	2A		IVR+LIO		0.6	0.6	8
23	M	2	OD	2A		IVR				17
24	M	14	OD	4A		LSV+PC+IVR+SO		0.05	NLP	56
			OS	3B		LSV+PC+CRO+IVR+SO		0.05	LP	57
25	M	12	OS	3B	+	LSV+PC+IVR		0.15	0.2	45
26	F	2	OS	3A		IVR	SB+CRY+IVR (4B)(2)			2
27	F	10	OD	3B	+	IVR	LSV+PC+IVR (3A)(0.25)	LP	0.1	10
28	F	2	OS	2B		IVR	SB+CRY+IVR (3A)(1)			11
29	M	5	OD	2B	+	IVR	LSV+PC+IVR (3B)(3)		0.6	12
30	M	0.3	OD	3A	+	LSV+PC+IVR			0.2	27

[a]3 IVR. VH: Vitreous hemorrhage; LSV: Lens-sparing vitrectomy; L&V: Lensectomy and vitrectomy; CF: Counting fingers; SB: Scleral buckle; PC: Photocoagulation; VA: Visual acuity; NLP: No light perception; LP: Light perception; IVR: Intravitreal ranubizumab; CRO: Cryotherapy; SO: Silicone oil; LIO: Laser indirect ophthalmoscopy.

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