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Outcomes of combined treatments in patients with retinal arterial macroaneurysm

Chenghu Wang, Guofan Cao, Xiangzhong Xu, Jian Wang[1], Shu Zhang

Purpose: To evaluate the outcome of the combined approach between intravitreal ranibizumab (IVR) and focal laser photocoagulation (FLP) in the treatment of symptomatic retinal arterial macroaneurysm (RAM). **Methods:** A total of 10 patients were included in this clinical case series report. They were diagnosed with symptomatic RAM (one eye in each) and assessed by a comprehensive ophthalmologic examination, including fluorescein angiography (FA), optical coherence tomography angiography (OCT-A), and indocyanine green angiography (ICGA). All patients were treated with an IVR followed by an FLP 2 weeks later. If necessary, a second IVR was given 1 month after the first one (or 2 weeks after the first FLP), which was followed by a second FLP treatment 2 weeks later in the needed cases. All cases were followed up for 6 months after the last treatment. **Results:** Both the retina hemorrhage and edema were resolved by the treatment. No ocular and/or systemic side effects were evident, and no recrudescence of RAM was seen within the 6 months of follow-up. **Conclusion:** The combined treatment of IVRs and FLPs was successful in the management of symptomatic RAM.

Key words: Atherosclerosis, focal laser photocoagulation, hypertension, intravitreal ranibizumab injection, retinal arterial macroaneurysm

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Retinal arterial macroaneurysms (RAMs) are acquired, focal dilations of a retinal artery, usually occurring within the first 3 bifurcations of the central retinal artery.[1] RAM is the result of a focal blood vessel weakness due to both aging and atherosclerosis.[2] The dilation occurs as the result of the blood vessel weakness and the raised hydraulic pressure seen in hypertension.[2] The associated pathologies include capillary telangiectasias, vascular remodeling, and retinal edema. While previous studies reported that asymptomatic RAMs can resolve spontaneously without significant sequelae,[3,4] early treatment is considered necessary in the symptomatic cases where subretinal hemorrhages, macular edema, and macular deposition of hard exudates are evident.[2]

However, currently, there is no protocol or guideline for the management of RAM. Several options are available for the treatment of RAMs with varied outcomes.[5-7] Focal laser photocoagulation (FLP) has been used in the treatment of RAMs for many years, which can be performed directly to the body of RAMs for promoting involution or decreasing leakage, or indirectly to the adjacent area around the RAMs for stopping or decreasing the progression of leakage toward the macula.[8-14] Currently, there is no defined criterion for when and how this treatment should be used. Many complications can occur after the FLP treatment, including large scar, choroidal neovascularization, and subretinal fibrosis.[14] Another major method for the treatment of RAM, which is developed more recently, is the intravitreal injection of anti-vascular endothelium growth factor (anti-VEGF).[15-18] Ranibizumab is one of the typical anti-VEGF antibodies, which can reduce the edema in RAM pathology and alter the balance between coagulation and fibrinolysis, and therefore, facilitate the clearing of retinal hemorrhage.[19,20] Therefore, it is efficient in the treatment of RAM. However, due to its short lifetime (50% clearance in 9 days in vitreous bodies),[21] repeated injections are required to maintain the treatment effect,[22] which is not acceptable due to the high cost and the risk of intraocular infection.[23]

To reduce the side effect and the need for repeated applications, intravitreal ranibizumab (IVR) injection has been used in combination with FLP in treating many fundus diseases that have abnormal tissue growth and/or edema.[8,16,24-31] The two methods appear to be complementary in that IVR can shrink the new growth and reduce the edema so that the FLP can reach the therapeutic effect with a lower dose; while the FLP would help to maintain a long treatment effect so that repeated IVR injects will not be necessary. Therefore, the combination of the two methods appears to produce a better treatment effect and few side effects than each of the two methods applied alone.[25,27-29] In a recent report, such a combination was used in the treatment of RAMs.[8] In this report, however, FLP was applied prior to the anti-VEGF treatment. The logic underneath

Affiliated Eye Hospital of Nanjing Medical University, Nanjing, China, [1]School of Communication Science and Disorders, Dalhousie University, Halifax, Canada

Correspondence to: Dr. Shu Zhang, Affiliated Eye Hospital of Nanjing Medical University, Nanjing 210029, China. E-mail: zhangs60@aliyun.com

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this sequence is not clear. In the present report, we presented 10 cases in which RAM was treated with a combination of IVR and FLP, in which IVR was applied in advance of FLP to fully utilize the complementarity between the two methods.

Methods

The study protocol and informed consent were approved by the Ethical Committee of the Affiliated Eye Hospital of Nanjing Medical University, China. Informed consent was obtained from the patients in accordance with the tenets of the Declaration of Helsinki.

This retrospective report covered 10 cases. One eye in each case suffered from symptomatic RAM. They were diagnosed and treated in the Affiliated Eye Hospital of Nanjing Medical University, China, between November 2015 and August 2019. The diagnosis of RAM was based on the results of the fundus examination. Fluorescein angiography (FA) and indocyanine green angiography (ICGA) were also performed, which are useful to visualize the hemorrhage blocks of the RAM.[5,6,32-36] The inclusion criteria were the presence of a symptomatic RAM with exudation and/or hemorrhage involving the fovea, as well as vision loss. Comprehensive ophthalmologic examinations were performed before the treatment, and monthly thereafter, including optical coherence tomography angiography (OCT-A) by which the RAM and the associated fluid accumulation, the blood flow in the different layers of the retina and choroids, the central macular thickness (CMT) were measured and quantified, the best-corrected visual acuity (BCVA) for visual function, and several other routine tests were carried out.

IVRs (Lucentis® 0.5 mg/0.05 mL; Novartis Pharma Schweiz AG, Switzerland) were initiated within 1 week after the RAM was diagnosed, except for two cases to which the treatment was delayed by 1–3 years. FLP was carried out 2 weeks after the initial IVR. If the submacular fluid remained evidenced under the OCT scanning after the first treatment, the IVR was repeated with an interval of 1 month, which was followed by a secondary FLP 2 weeks after the second IVR (or 1 month after the first FLP). The laser of 577 nm (Supra Scan from Quantel Medical, Cournon-d'Auvergne, France) was applied with 100–200 μm in diameter, 0.15–0.20 s in exposure duration and 100–200 mW in power. The dose of the laser (power X duration) was adjusted to reach a gentle retinal whitening surrounding the RAM. Each laser treatment was started from the peripheral region and progressively narrowed toward the center of the RAM to produce atrophy of RAM gradually.

Results

Table 1 summarizes the main characteristics of the patients and the outcomes. This sample included one male and nine female subjects. The age of the group was 62.9 ± 9.8 years. Every patient suffered from a long history of hypertension and every involved eye had various degrees of preretinal and/or intraretinal hemorrhage, with or without serious retinal detachment. The effectiveness of the treatment was demonstrated by a significantly reduced CMT, from the baseline median value of 524 (392.5, 530) μm to the final median value of 200 (187.5, 202.5) μm tested at the last follow-up (Wilcoxon signed rank tests, $Z = -2.807$, $P = 0.002$). The visual function was quantified by the logarithm of the minimal angle of resolution (logMAR) that was calculated from the BCVA, Table 1). No significant improvement in the visual function was seen in this sample as a group (Wilcoxon signed rank tests, $Z = -1.899$, $P = 0.055$), although the improvement was seen in several cases. No complications, such as endophthalmitis, traumatic lens injury, or retinal detachment, were encountered in any case in this sample.

Below are the representative images from individual subjects taken from the process of the treatment. Fig. 1 shows several typical appearances of fundus photograph that were taken before the treatment (from cases 3[Fig. 1a], 5[Fig. 1b], 7[Fig. 1c], 8[Fig. 1d], respectively). Those images feature a dilation of retinal arterial branches with surrounding bleeding and stellate-shaped exudates around it. Based upon those images, the RAM can be easily diagnosed. Figs. 2 and 3 are the OCT-A images obtained from case 6, a 59-year-old female, who was diagnosed with RAM in November 2015 but was not treated until February 2019. Her BCVA was 0.05 before the treatment. In the OCT-A scan, her RAM was found supratemporally to the macula in the left eye [Fig. 2a]; the local blood circulation was interrupted by the RAM across an area approximately 400 μm in diameter [Fig. 2a and c]. She received two IVRs and two laser treatments within 2 months. The OCT-A scan 1 month after the last treatment showed that the RAM was largely shrunk [Fig. 2d], and the local blood circulation was re-established [Fig. 2b]. Fig. 3 shows the reduction of the submacular fluid by the treatment in this case. The result demonstrated the success of the RAM treatment: The submacular fluid was largely reduced 40 days after the first IVR treatment [Fig. 3b and e] and remained unchanged later [Fig. 3c and f]. However, the visual function was not improved, which was probably due to the long delay of the treatment after the RAM was initially formed. Fig. 4 presents the OCT-A images from case 7, who is an example of a good rescue of visual function after prompt treatment. This 54-year-old female visited our hospital because of vision reduction and metamorphopsia in her left eye for a week. The examination showed that her baseline BCVA was 0.015. The OCT-A scan showed a large amount of submacular fluid [Fig. 4a and d]. The diagnosis of RAM was confirmed by the fundus photograph [Fig. 1c] and FA. This patient was treated 1 day after the diagnosis of RAM. The submacular fluid was largely reduced in the OCT-A scan [Fig. 4e] and the fundus hemorrhage decreased significantly [Fig. 6] 15 days after the surgery and totally resolved 71 days after the first treatment [Fig. 4f]. Her final BCVA was improved to 0.25 as tested 6 months after the first treatment. Fig. 5 presents the OCT-A images from case 2 in which substantial damage of the macular structure was evident by the much-reduced thickness and the discontinuity of the sensorial epithelia [Fig. 5b]. In this case, no recovery in the visual function was found, even though the treatment was done shortly after the diagnosis of RAM.

Discussion

In the present report, a total of 10 cases of RAM were presented. Although the prevalence of this disease is low, the diagnosis is not difficult based upon the clinical symptoms and the imaging examinations (fundus photograph [Fig. 1] and OCT-A scan [Figs. 2–4]). Out of the 10 cases, 9 were females, suggesting a much higher prevalence in females. All of them had a long history of blood hypertension. Those two features are consistent with other reports.[2,8,37]

Table 1: Characteristics of patients with RAM

Case number	Age	Sex	Medical History	Macular	Lesion Location	Treatments	BCVA (LogMAR)		CMT (μm)	
							Baseline	Final	Baseline	Final
1	61	F	HT	IRH SRD	infra-Temporal, OS	2 IVRs + 2 FLPs	0.92	0.4	520	210
2	78	F	HT	IRH, RD	infra-Temporal, OD	2 IVRs + 1 FLP	0.92	0.82	528	220
3	65	F	HT, DM	PRH,	supra-Temporal, OD	1 IVR + 1 FLP	0.52	0.3	220	200
4	78	F	HT	IRH, SRD	infra-Temporal, OS	1 IVR + 1 FLP	1.7	1.82	200	180
5	55	F	HT	IRH, SRD	supra-Temporal, OD	1 IVR + 1 FLP	0.52	0.4	470	200
6	59	F	HT	IRH, PRH, SRD	supra-Temporal, OS	2 IVRs + 2 FLPs	1.3	1.3	536	190
7	54	F	HT	IRH, PRH, SRD	infra -Temporal, OS	2 IVRs + 2 FLPs	1.82	0.6	450	200
8	71	F	HT	IRH, SRD	supra-Temporal, OS	2 IVRs + 2 FLPs	0.52	0.4	528	200
9	51	M	HT	IRH, PRH, SRD	infra-Temporal, OD	2 IVRs + 2 FLPs	0.82	0.6	550	180
10	57	F	HT	IRH, SRD	supra-Temporal, OS	1 IVR + 1 FLP	0.82	0.92	528	200

BCVA - best-corrected visual acuity; PRH - preretinal hemorrhage; IRH - intraretinal hemorrhage; SRD - serous retinal detachment; CMT - central macular thickness; HT - hypertension; DM - diabetes mellitus; OD - right eye; OS - left eye; IVR - intravitreal ranibizumab; FLP - focal laser photocoagulation

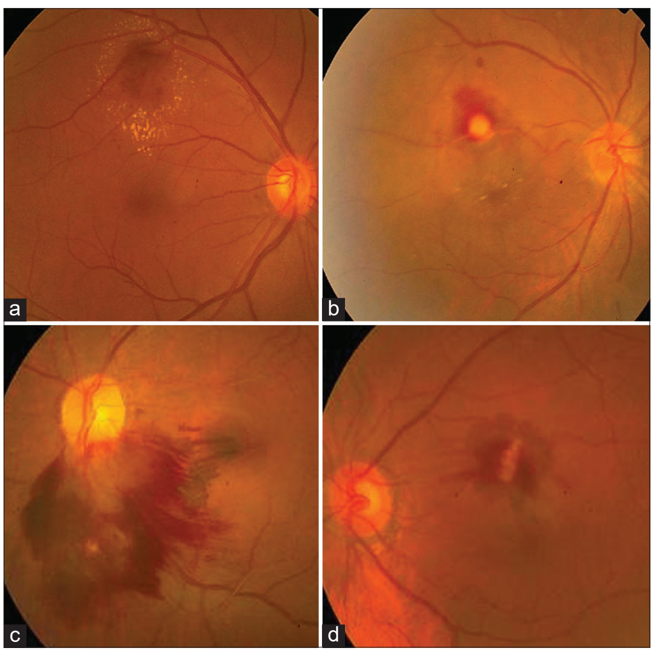

Figure 1: The fundus photographs from case numbers 3, 5, 7, and 8 before the treatment

Due to its rareness, RAM was often misdiagnosed 20–30 years ago. But, with more cases accumulated, RAM should not be missed based upon its typical appearances in the fundus photograph [Fig. 1]. It features a dilation of retinal arterial branches with bleeding and/or stellate-shaped exudates around it. FA can help in a differential diagnosis from other diseases, such as age-related macular degeneration (AMD) and proliferative diabetic retinopathy (PDR).[2,5,6,8,32-37] It is especially useful in differentiating fusiform RAMs from saccular RAMs. In the cases where hemorrhage blocks visualization of RAM in fundus photograph and the diagnosis with FA image is also not conclusive, ICGA is especially beneficial in that it can pinpoint the exact location of the RAM in such cases.[5,38-45] In the present report, all cases were clearly and correctly diagnosed by using all those methods. We think that an organic combination of those methods can guaranty the diagnosis.

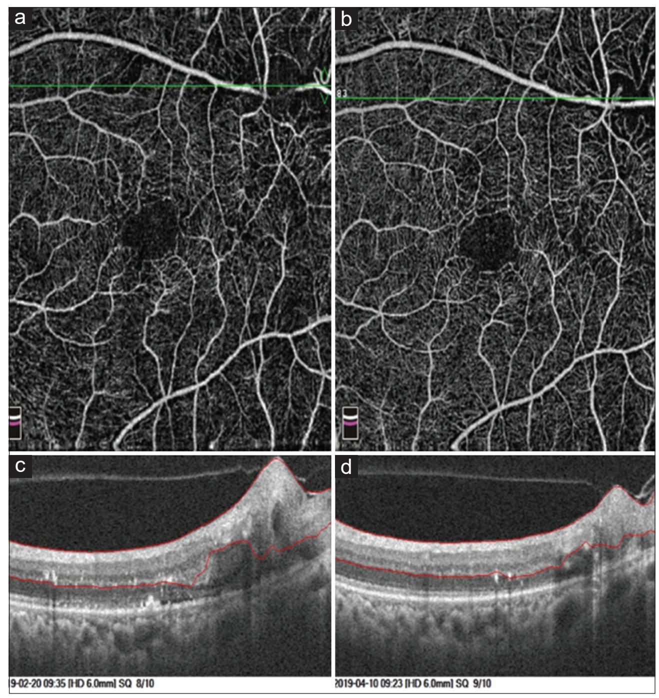

Figure 2: OCT-A scan images from case 6 a and b: OCT-A images of the retina slab. The lines in the inserted squares show the depth of the OCT-A scan; c and d: The images of spectral-domain optical coherence tomography (SD-OCT); a and c: The images taken before the treatment; b and d: The images after the treatment; The lines in a and b went across the location of the RAM on the right corner, where the signal of blood flow was interrupted before the treatment (a), but fully recovered after the treatment (b); Correspondingly, the reduction of the RAM was demonstrated by the difference between c and d

The strategy for RAM management has not been optimized, and currently, there is no guideline or regulated protocol. Several methods have been showing effectiveness in the treatments of RAM;[5,7,20] among them, IVR and FLP appear to be more attractive.[11,12,17,19,20] More importantly, these two treatments appear to be complimentary. As reported in the treatment of diseases such as PDR,[5,25,28,46-48] the combination of the two reduces the side effects and the required number of treatments as compared to the application of each method

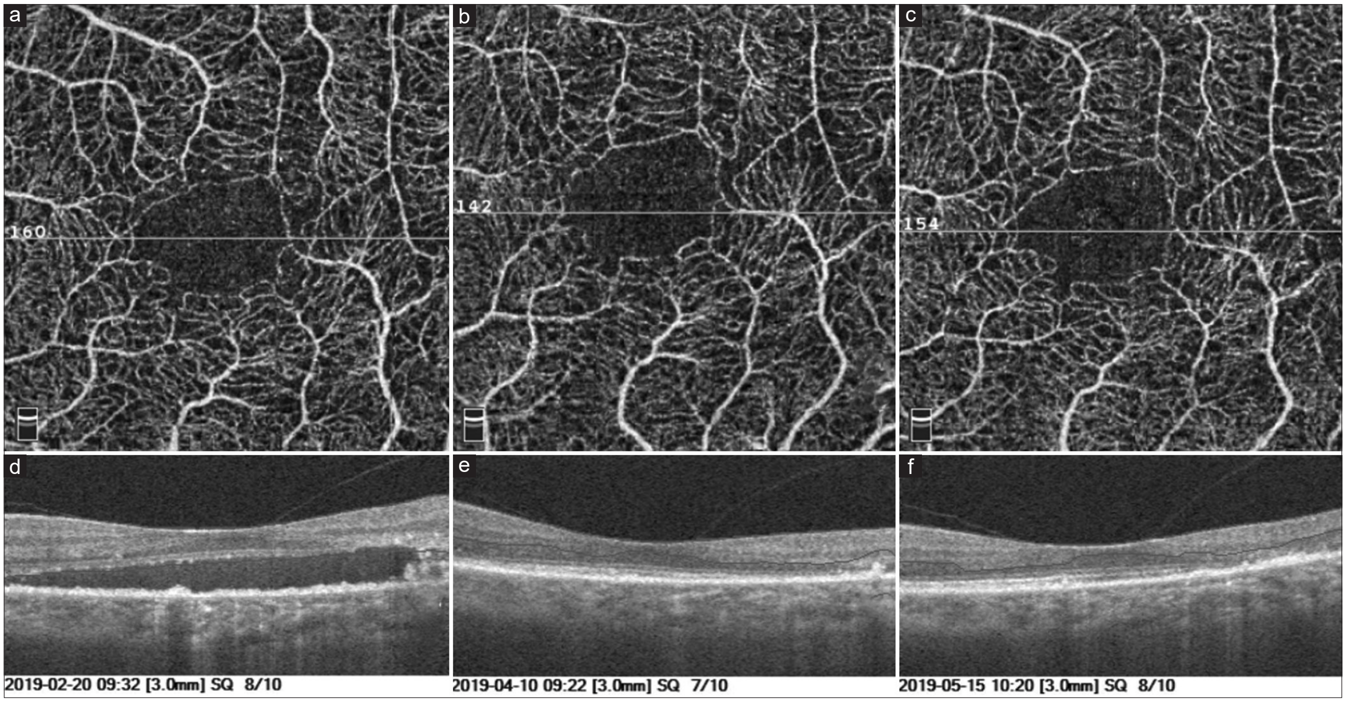

Figure 3: Multiple OCT-A of macular views from case number 6 (a, b and c): macular view of the retina slab; (d, e and f): SD-OCT views across macula; (a and d): Images before the treatment; b and e: 40 days after the first treatment; c and f: 76 days after the first treatment; the accumulated submacular fluid seen before the treatment (d) was largely reduced in (e) and remained unchanged in (f)

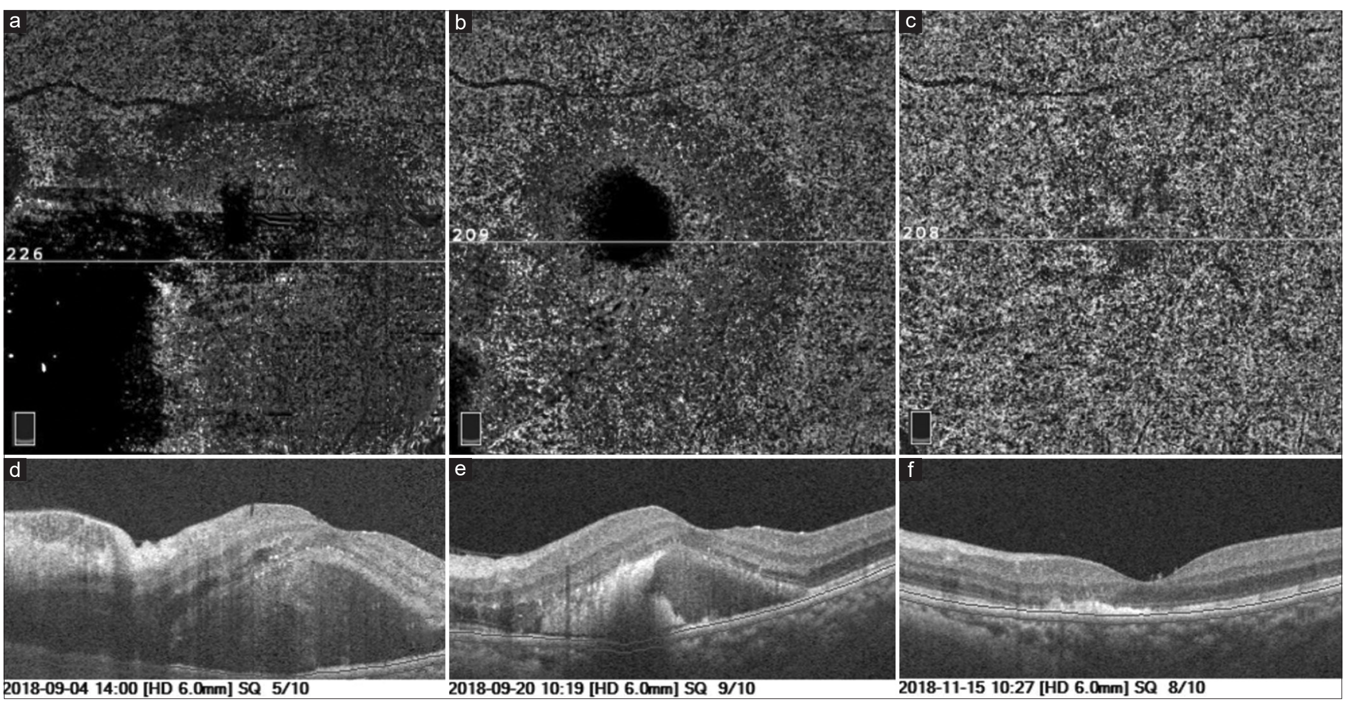

Figure 4: Multiple OCT-A images across the macula from case number 7 (a, b, and c) macular view of the retina slab; (e, f, and g) SD-OCT views showing the change of submacular fluid; (a and d): The images taken before the treatment; (b and e): the images taken 15 days after the first treatment; (c and f): The images taken 71 days after the first treatment; the fluid was largely reduced in e and totally resolved in f

alone.[5] In the present report, we applied IVR first based upon the assumption that the IVR treatment would significantly reduce the edema and the growth of the blood vessel so that the laser dose could be reduced. This assumption is supported by previous studies in the treatment of PDR.[48] In addition, a delay (2 weeks) between IVR and FLP was employed. This allowed the effect of IVR in reducing edema to be fully showed off and further help for the use of FLP

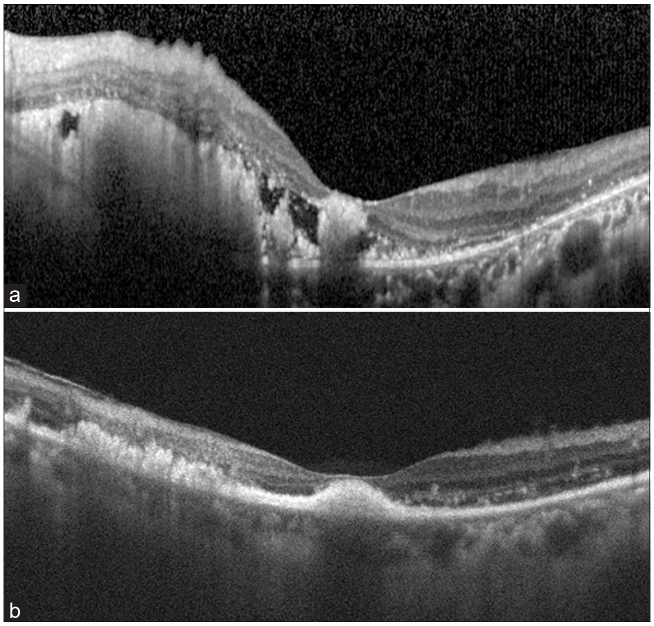

Figure 5: OCT-A scan taken before (a) and 1 month after (b) the first IVR in case 2. Although submacular fluid was largely reduced, the macular structure damage remained as demonstrated by the reduced thickness and discontinuity

Figure 6: Fundus image from case number 7. The image taken 15 days after the first treatment; the fundus hemorrhage decreased significantly

at a lower dose. This was consistent with the other studies in which the severity of RAM was stabilized in patients undergoing IVR injections for retinal edema.[19] The lower dose of FLP should have reduced the risk of the side effects of FLP.[49] Overall, a good outcome was reached in the present sample. In every case, the RAM virtually disappeared by the treatment and no reoccurrence was seen. However, the good outcome should not rule out the possibility that the protocol used in this study was not optimized. This could not be done in the present study due to limited case numbers.

In the present report, no improvement of visual function was seen in general after the treatment. This null result may be due to the long-term exudative manifestations, especially involving hemorrhage, which may lead to progressive photoreceptor deterioration and permanent impairment. This has been seen in cases 4 and 6, in which the first treatment began from 1 to 3 years after the RAM was diagnosed. Besides, if the RAM was found already with the damage of the macula structure, which was the case as shown in Fig. 5, despite the treatment was promptly done after the diagnosis, however, the structural damage to the macula appeared to be not recoverable. In such cases, visual acuity deterioration could not be stopped, and the loss of visual function may not be rescued even by prompt treatment.

The protocol used in this report may not be optimized. The rareness of this disease makes it difficult to have multiple groups for a comparison of different protocols.

Conclusion

The combination of IVR and FLP is effective in the treatment of symptomatic RAM. The diagnosis of RAM is feasible and prompt treatment is desirable. The protocol should be optimized in a larger sample. The long-term effects need to be confirmed by a longer follow-up.

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Conflicts of interest

There are no conflicts of interest.

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