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Commentary Open Access

Intravitreal Vascular Endothelium Growth Factor Inhibitors for Retinal Macroaneurysms

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Abstract

Last year our group published the case of a foveal longstanding retinal macroaneurysm successfully treated with intravitreal ranibizumab. Few studies have also reported the safety and effectiveness of intravitreal vascular endothelium growth factor inhibitors (anti-VEGF) in the management of symptomatic retinal arterial macroaneurysms. In this commentary we make a brief review of this clinical entity, particularly of its complications and its management with emphasis on anti-VEGF therapy.

Keywords: Retinal arterial macroaneurysm; Intravitreal vascular endothelium growth factor inhibitors; Anti-VEGF

Commentary

Retinal arterial macroaneurysms (RAMs) are uncommon, acquired, focal dilatations of the arterial wall usually associated with advancing age, female gender and systemic vascular pathology such as hypertension, dyslipidaemia and atherosclerosis [1-3]. They occur most often in the macular or post-equatorial regions, in the first three orders of the arterial tree, where the perfusion pressure is higher and the arterial sac is more easily perforated [1-3]. Arteriovenous crossings are at increased risk of aneurysm formation due to the absence of the adventitial layer, which compromises the structural support [3].

Since 1987, RAMs have been classified according to their predominant clinical behaviour as exudative, haemorrhagic or quiescent. [3]. Exudative RAMs cause macular edema and hard exudates leading to vision loss if they are close to the fovea; haemorrhagic RAMs bleed to subretinal, intraretinal, retrohyaloidal or vitreal spaces; and quiescent RAMs are usually asymptomatic but they can complicate with both exudates and haemorrhage.

Multimodal imaging with fluorescein angiography (FA), indocyanine green angiography (ICGA) and optical coherence tomography (OCT) is important in the initial assessment of a patient with a RAM, both in the diagnosis and classification [4,5]. In exudative RAMs, FA shows dye exudation around the lesion. In haemorrhagic cases, ICGA is sometimes necessary to identify the RAM since it avoids the shadow effect of blood and to exclude other causes of haemorrhage such as choroidal neovascularization. Video-angiography shows the pulsatility of the RAM. OCT allows the monitoring of RAM occlusion, spontaneously or after treatment, the classification of the haemorrhage and edema as pre, intra or subretinal and the monitoring of macular edema, central macular thickness (CMT) and complications such as atrophy and fibrosis.

The visual impact of a RAM depends on its distance to the fovea, on its clinical behaviour and, mainly, on whether or not the fovea is committed. RAMs usually resolve spontaneously with gradual thrombosis and subsequent fibrosis [1]. Therefore, given its benign clinical course, it is generally accepted that both quiescent and asymptomatic RAMs that do not threaten the fovea do not require treatment and should be kept under surveillance [1]. However, there is no established treatment protocol when RAMs complicate. Despite the fact that symptomatic RAMs can obliterate spontaneously with functional recovery [1,5], it is also known that long-term persistence of both retinal edema and haemorrhages are established causes of progressive retina damage with irreversible photoreceptor loss and functional impairment [1,6]. Hence, there has been a growing tendency to treat sooner both asymptomatic RAMs that threaten the fovea and symptomatic RAMs.

Multilevel retinal haemorrhage is a non-infrequent complication of haemorrhagic RAMs [1,7]. The worst prognosis is associated with significant subretinal haemorrhages, which severely and promptly damage the overlying retina with irreversible photoreceptor degeneration being established in two weeks [8,9]. Foveal submacular haemorrhages have been successfully treated with vitrectomy and pneumatic blood displacement with intravitreal or subretinal injection of recombinant tissue plasminogen activator [1,7]. The second approach is our preferred one in this particular situation. On the other hand, bleeding in the retrohyaloidal and vitreous compartments is associated with good prognosis. However, in case of persistent retrohyaloidal or vitreous haemorrhage, hyaloidotomy with Nd: YAG (Neodymium: yttrium-aluminium-garnet) laser or vitrectomy, respectively, can be used [1,7].

The most popular therapeutic intervention to treat RAMs is laser photocoagulation. Direct and indirect modalities, either with threshold or sub-threshold settings have been used successfully [1,7,10]. However, laser therapy outcomes are controversial and there have been reports of vision loss due to laser-induced retinal damage, caused by an early increase in exudates from selective reabsorption of fluid and late complications such as epiretinal membranes, choroidal neovascularization and chorioretinal scar enlargement [1,3]. In spite of these risks, laser treatment should be considered judiciously in each particular case to seal both RAM and its adjacent leaky vessels [9,10].

Intravitreal vascular endothelium growth factor inhibitors (anti-VEGF) usage is widespread in Ophthalmology practice, mostly in the treatment of posterior segment pathologies such as macular edema,

retinal neovascularization, retinal vein occlusion and choroidal neovascularization, to name only the most frequent and well supported.

Intravitreal bevacizumab (Avastin®) and ranibizumab (Lucentis®) have been reported since 2009 with excellent outcomes in the treatment of patients with symptomatic RAMs (Table 1). Both drugs are IgG antibodies, respectively a full-length antibody and an antibody fragment, that block the action of all VEGF-A isoforms. Although they seem to be effective in both sealing RAMs and improving macular edema and visual acuity [11], the mechanism of action of anti-VEGF therapy in RAMs is still not fully understood. Given the fact that Aflibercept (Eylea®) has a similar mechanism of action, it may also be potentially effective in this context.

Arterial focal ischemic damage and the subsequent VEGF upregulation are thought to be responsible for the increase in permeability and dilation that occur in RAMs [12,13]. VEGF induces vasodilation through the production of nitrous oxide and modulates both angiogenesis and thrombosis through its action in VEGF receptors type 1 and type 2, respectively [14]. Anti-VEGF drugs not only decrease VEGF levels but also decrease VEGF receptor type 1 levels and increases VEGF receptor type 2 levels [15]. As a result, anti-VEGF may reduce edema by blocking the VEGF-induced vascular permeability and inducing thrombosis by changing the coagulation process itself, without locally destructive side effects [8,11,15,16]. Anti-VEGF drugs may also enable a faster reabsorption of haemorrhages and can be an option in cases of subtle subretinal haemorrhages [4,17].

Article´s first author	Year of publication	Anti-VEGF molecule	Clinical Form	Number of patients	Pre-BCVA	Post-BCVA	CRT improvement (µm)	RAM Closure Rate	Mean number of injections	Follow-up (months)
Chanana [22]	2009	Bevacizumab	Exudative	1	20/400	20/50	607 → 173	100%	2	1.5
Jonas [23]	2010	Bevacizumab	Exudative	1	20/400	20/200	"Completely absorbed"	100%	1	3
Javey [20]	2010	Bevacizumab	Haemorrhagic (Multi-level haemorrhage)	1	20/400	20/20	-	100%	2	12
Wenkstern [24]	2010	Ranibizumab + laser	Exudative	1	20/50	20/25	510 → 148	100%	2	5
Golan [25]	2011	Bevacizumab	Exudative	1	20/160	20/20	364 → 242	-	2	13
Tsakpinis [21]	2011	Bevacizumab	Haemorrhagic	1	20/60	20/25	-	100%	2	39
Zweifel [26]	2013	Bevacizumab + ranibizumab	Exudative	10	20/100	20/50	366 → 266	100%	3	6
Cho [18]	2013	Bevacizumab	Haemorrhagic (n=17) Exudative (n=6)	23	20/80	20/60	384 → 265	-	1.4	11
Pichi [11]	2013	Bevacizumab	Haemorrhagic (n=19) Exudative (n=18)	37	20/75	20/25	520 → 214	94,7%	3	3
Leung [16]	2015	Bevacizumab + laser	Exudative	1	20/60	20/30	312 → 241	100%	6	20
Menezes [19]	2015	Ranibizumab	Exudative	1	20/200	20/50	310 → 233	100%	6	12
Erol [27]	2015	Ranibizumab	-	7	20/245	20/30	427 → 208	100%	2	19
Cahuzac [4]	2016	Ranibizumab or ranibizumab+ laser (*)	Haemorrhagic (5) Exudative (1)	6	20/400	20/40	869 → 255	100%	-	6

Table 1: Literature review of anti-VEGF therapy in RAM. BCVA: Best Corrected Visual Acuity; VEGF : Vascular Endothelial Growth Factor: CRT: Central Retinal Thickness; (*): one case also with concomitant Nd: YAG hyaloidotomy.; (-): cases in which data is not available.

From 2009 till the beginning of 2016 at least 91 cases have reported the usage of anti-VEGF therapy in the management of RAMs, the biggest majority (84 cases) without concomitant laser treatment (Table 1). After the analysis of these cases, it was shown that an average number of 2,5 intravitreal anti-VEGF injections are effective with significant resolution of serous detachment and macular edema as can

be evaluated by CRT, almost complete RAM closure rate and functional improvement with increase of best-corrected visual acuity (BCVA). In fact, these outcomes are undoubtedly promising. BCVA (in decimal scale) improved in all cases, from around 0,21 preoperatively to 0,59 at the end of follow-up. No cases of visual acuity loss, local or systemic complications related to the treatment were reported in any of the published cases.

Pichi et al. developed a prospective non-comparative study, with the largest case-series published and found that bevacizumab is effective in sealing almost all RAMs with rapidly improvement BCVA and CRT after 3 intravitreal injections in all patients [11]. Cho et al., in a comparative prospective non-randomized study, found a more rapid and better visual improvement and macular edema resolution in the bevacizumab treated group in relation to the control group, which was significant at 1 month but not at 3 months of follow-up [18]. This fact was attributed to the small number of eyes included in the statistical analysis. Our group presented a case of a patient with a longstanding exudative RAM within the avascular perifoveal zone, unsuitable for laser treatment, which was successfully treated with six ranibizumab intravitreal injections [19]. Other groups published the successful usage of anti-VEGF in predominantly haemorrhagic RAM, some of them with submacular involvement, namely a faster haemorrhage reabsorption and functional improvement [4,11,18,20,21].

The use of anti-VEGF agents has been suggested as a mean of achieving a rapid resolution of RAMs with a limited rate of complications. However, bevacizumab, ranibizumab and, potentially, aflibercept are off-label intravitreal injections in this indication and the risk-benefit ratio must be explained to patients.

Our algorithm in the approach to a patient with a RAM, with emphasis on anti-VEGF therapy, is the following:

- Quiescent RAMs may be observed every six to twelve months with dilated fundoscopic examinations and an internist should evaluate the patient with emphasis on hypertension control.
- Exudative or haemorrhagic RAMs that do not threaten the fovea may be monitored every one to three months with the same procedure and with the aid of OCT.
- If RAMs show features of involution in FA or OCT and the foveal commitment is not severe, the patient may be observed for at least two months for the exudates and haemorrhages to involute before considering treatment.
- If active RAM exudates or haemorrhage threaten or involve the fovea we propose early treatment with laser or anti-VEGF.
- Anti-VEGF is our first choice in cases of extensive exudation or haemorrhage around the RAM and in cases in whose location may be less advisable for laser therapy such as the fovea or a major or macular vessel.
- Although, in our opinion, the treatment of a severe central submacular haemorrhage should be urgent and surgical, the treatment of less severe or extrafoveal cases and non-self-limited retinal or vitreous haemorrhages may be also treated with anti-VEGF to hasten the recovery.

Intravitreal anti-VEGF therapy may, in our opinion, represent a changing paradigm in the approach to RAMs not amenable to laser treatment due to its location, severity, chronicity or refractoriness. However, future prospective randomized and controlled studies are necessary to corroborate these results and longer periods of follow-up may help to understand the clinical progression of these patients. Besides recognizing an important role of VEGF in RAMs treatment is still to investigate the exact molecular pathways involved.

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