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Clinical Outcomes of Retinal Arterial Macroaneurysms With Vitreous Hemorrhage Treated With Observation, Antivascular Endothelial Growth Factor Intravitreal Injections, or Pars Plana Vitrectomy

Sophia S. Lam, BS[1], Abtin Shahlaee, MD[2], Mirataollah Salabati, MD[2], and Michael A. Klufas, MD[2]

Abstract

Purpose: To evaluate the clinical outcomes of different types of treatment of retinal arterial macroaneurysm with vitreous hemorrhage. **Methods:** This retrospective cohort study comprised patients with retinal arterial macroaneurysm and vitreous hemorrhage who were examined at a single retina clinic between 2013 and 2021. **Results:** Treatment arms included observation (n = 33), intravitreal injections (IVIs) of antivascular endothelial growth factor agents (n = 5), and pars plana vitrectomy (PPV; n = 12). Baseline characteristics and final best-corrected visual acuity (BCVA) were similar in a combined analysis of all treatment groups ($P > .05$). The BCVA improved in all eyes, but the IVI and PPV arms had worse presenting BCVA. The mean number of injections was 3.6 ± 2.8. The incidence of subretinal hemorrhage was 18.2% in the observation arm, 25.0% in the PPV group (8.3% had subretinal tissue plasminogen activator), and 60.0% in the IVI group. The mean time to intervention was 13 ± 15.3 days for PPV and 38 ± 69.9 days for IVI. There was no correlation between the number of injections and the final BCVA ($r = 0.13$, $P = .830$). The IVI and PPV arms were more frequently on anticoagulants ($P = .011$). There was no difference in final BCVA between those using anticoagulants (0.52 ± 0.53) vs not using anticoagulants (0.55 ± 0.65) ($P = .870$). **Conclusions:** Most patients, regardless of treatment modality, demonstrated significantly improved BCVA and similar final visual outcomes. Patients with worse presenting BCVA were more likely to undergo PPV or IVI whereas those with better presenting BCVA had excellent outcomes with observation alone. Improved BCVA was not associated with the number of IVIs or anticoagulant use.

Keywords

anti-VEGF agents, lasers, retinal vascular disease, vitreous hemorrhage, vitreoretinal surgery

Introduction

Retinal arterial macroaneurysms (RAMs) are localized dilations of retinal arterial branches often found in the temporal retina, usually along the supero- or inferotemporal arterioles. Risk factors for RAM include female sex, age older than 60 years, systemic hypertension, and arteriosclerotic vascular disease.[1] Common presenting symptoms include acute vision loss from macular edema or retinal and/or vitreous hemorrhage (VH) secondary to thrombotic end-arteriole occlusion or aneurysm rupture.[1] Patients may also present with associated capillary telangiectasias, vascular remodeling, retinal edema and exudates, subretinal hemorrhage, and retinal detachment.

Most RAMs are self-resolving with a good visual prognosis but may have concurrent hemorrhages into the vitreous, intraretinal, subretinal, or preretinal areas. Vitreous or preretinal hemorrhages have a good visual prognosis, but submacular hemorrhages have a poorer prognosis and can lead to severe vision loss if left untreated.[1]

Various types of treatment manage RAMs based on their clinical appearance and associated complications. Most patients with asymptomatic or symptomatic RAMs with vision loss secondary to intraretinal, preretinal, or VH can be observed for spontaneous resolution.[1] In cases in which there is an increased risk for photoreceptor cell damage or an obscured view of the

[1] Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA
[2] Mid Atlantic Retina, Retina Service of Wills Eye Hospital, Philadelphia, PA, USA

Corresponding Author:
Michael A. Klufas, MD, Mid Atlantic Retina, Retina Service of Wills Eye Hospital, 840 Walnut St, Ste 1020, Philadelphia, PA 19107, USA.
Email: mklufas@midatlanticretina.com

underlying retina that makes it difficult to monitor the RAM, further interventions such as laser photocoagulation or intravitreal injections (IVIs) of antivascular endothelial growth factor (anti-VEGF) agents may be used. Pars plana vitrectomy (PPV) may be considered for RAMs with persistent VH after an observation period or for earlier removal of preretinal blood for macular visualization or faster visual improvement.[1] The presence of a macular subretinal hemorrhage may require subretinal injection of recombinant tissue plasminogen activator (tPA) during PPV to improve visual outcomes.[2]

Few studies have directly compared the various treatments of RAM with VH.[3] This study aims to identify the patient characteristics and clinical outcomes of RAM with VH through a retrospective comparative analysis of 3 treatment groups: observation, anti-VEGF IVI, and PPV.

Methods

This study was a retrospective analysis of patients with RAM and VH seen between July 2013 and October 2021 at Mid Atlantic Retina, the retina service of Wills Eye Hospital. Inclusion criteria were patients with a confirmed diagnosis of RAM and VH in the same eye who underwent 1 type of treatment, complete notes on their medical record, a follow-up of 30 days or more, and a comprehensive ophthalmologic examination (eg, slitlamp biomicroscopy with fundus examination). Patients were excluded if they had a VH without RAM, incomplete notes on their medical record, or multiple treatments such as a presurgical IVI before PPV. Patients with severe hypertensive retinopathy, diabetic retinopathy, retinal vein occlusion, or radiation retinopathy were also excluded.

The following patient characteristics were collected from each medical record: age at onset of diagnosis, sex (female/male), lens status at the onset of diagnosis (phakic, aphakic, or pseudophakic), time to first intervention in days calculated from the date between the first visit and first treatment, duration of follow-up period in days calculated from the first diagnosis and last visit, baseline best-corrected visual acuity (BCVA) in Snellen and logMAR, final BCVA in Snellen and logMAR, treatment type (observation, anti-VEGF IVI, or PPV), number and type of anti-VEGF IVI (bevacizumab, ranibizumab, or aflibercept), comorbidities (diabetes, hypertension, cardiovascular disease, thyroid disease, hypercholesterolemia/hyperlipidemia, or cerebrovascular disease), anticoagulation use (nonsteroidal anti-inflammatory drug, direct factor Xa inhibitor, P2Y12 inhibitor, direct thrombin inhibitor, vitamin K antagonist, or PDE3 inhibitor), and retinopathies (nonproliferative or proliferative diabetic retinopathy, severe hypertensive retinopathy, central or branch retinal vein occlusion, or radiation retinopathy).

Descriptive analyses of the patient characteristics were calculated for all patients. Comparative analyses were calculated after stratification of the 3 treatment groups. The comparative variables mean age, sex, phakic lens status, mean baseline and final BCVA, change in baseline and final BCVA, mean duration of follow-up period, and anticoagulant usage were measured. Other measured variables included the mean number and range of anti-VEGF IVIs, the correlation between the number of anti-VEGF IVIs and final BCVA, and the final BCVA between patients using anticoagulant agents and those who did not use these agents.

Statistical analysis was performed using SPSS software (version 24, IBM). One-way analysis of variance, chi-square, Fisher exact, Kruskal-Wallis, and Wilcoxon signed-rank tests were used to compare continuous and categorical variables. Statistical significance was set at $P < .05$.

Table 1. Baseline Characteristics of Patients With RAM and VH.

Variable	Value (50 Eyes, 50 Patients)
Lens status, n (%)	
Aphakic	1 (2)
Phakic	23 (46)
Pseudophakic	26 (52)
Treatment group, n (%)	
Observation	33 (66)
Anti-VEGF intravitreal injection	5 (10)
Pars plana vitrectomy	12 (24)
Anti-VEGF agent, n (%)	
Bevacizumab	100
Ranibizumab	0
Aflibercept	0
Total injections: mean ± SD (range)	3.6 ± 2.8 (1,8)
Comorbidity, n (%)	
Diabetes	6 (12)
Hypertension	23 (46)
Cardiovascular disease	13 (26)
Thyroid disease	7 (14)
Hyperlipidemia/hypercholesteremia	16 (32)
Cerebrovascular disease	3 (6)
Anticoagulant use, n (%)	
Aspirin	12 (24)
Clopidogrel	2 (4)
Dabigatran	1 (2)
Apixaban	3 (6)
Rivaroxaban	2 (4)
Warfarin	6 (12)
All anticoagulant use	23 (46)

Abbreviations: Anti-VEGF, antivascular endothelial growth factor; RAM, retinal arterial macroaneurysm; VH, vitreous hemorrhage.

Results

Of 192 available eyes and 186 patients, 50 eyes of 50 patients were included in the analysis. A total of 142 eyes were excluded. Four eyes were excluded for diagnosis of VH without RAM in the same eye, 4 eyes for incomplete data in the patient's medical record, 5 eyes for a follow-up less than 35 days, 117 eyes due to the presence of concomitant retinopathies, and 12 eyes for multiple treatments (eg, both IVI and focal laser). The descriptive statistics of the included patients are given in Table 1.

Table 2. Comparative Analysis Between Observation and Anti-VEGF IVI or PPV Treatment in Eyes With RAM and VH.[a]

Parameter	Observation (n = 33)	Anti-VEGF IVI (n = 5)	PPV (n = 12)	*P* Value	Total (50 Eyes, 50 Patients)
Age (y): mean ± SD (range)	73 ± 15	82.8 ± 7.8	79.4 ± 7.7	.150[b]	75.5 ± 13.1 (38,99)
Sex, female/male	20/13	2/3	8/4	.560[c]	Female: 30 (60%) Male: 20 (40%)
Baseline logMAR VA: mean ± SD (Snellen)	0.95 ± 0.83 (20/191)	1.5 ± 0.84 (20/632)	1.80 ± 0.85 (20/1262)	.0120[d]	1.23 ± 0.89 (20/340)
Phakic lens status, n (%)	17 (51.5)	2 (40)	4 (30.8)	.730[c]	23 (46)
Anticoagulant use, n (%)	11 (33.3)	2 (40)	10 (76.9)	.011[c]	—
Final logMAR VA: mean ± SD (Snellen)	0.53 ± 0.61 (20/68)	0.53 ± 0.82 (20/68)	0.56 ± 0.50 (20/73)	.390[d]	0.54 ± 0.59 (20/69)
Vision change (logMAR): mean ± SD	−0.42 ± 0.65 ($P < .001$)[e]	−0.98 ± 0.93 ($P = .068$)[e]	−1.24 ± 0.75 ($P = .003$)[e]	.009[d]	−0.68 ± 0.78 ($P < .001$)
Duration of follow-up (d): mean ± SD (range)	435 ± 70	478 ± 294	517 ± 570	.850[b]	459 ± 433 (35,1837)
Time to intervention (d): mean ± SD	NA	38 ± 69.9	13 ± 15.3	—	—
Incidence of subretinal hemorrhage, n (%)	6 (18.2)	3 (60)	3 (25) 1 (8.3) had tPA	—	—

Abbreviations: ANOVA, analysis of variance; anti-VEGF, antivascular endothelial growth factor; IVI, intravitreal injections; NA, not applicable; PPV, pars plana vitrectomy; RAM, retinal arterial macroaneurysm; tPA, tissue plasminogen activator; VA, visual acuity; VH, vitreous hemorrhage.
[a]Cells with dashes indicate the parameter was not analyzed.
[b]One-way ANOVA test of anti-VEGF IVI and PPV groups vs observation group.
[c]Chi-square or Fisher exact test of anti-VEGF IVI and PPV groups vs observation group.
[d]Kruskal-Wallis test of anti-VEGF IVI and PPV groups vs observation group.
[e]Wilcoxon signed-rank test of final vs baseline VA.

Table 3. Baseline vs Final VA in Eyes With RAM and VH Undergoing Observation, Anti-VEGF IVI, or PPV (50 Eyes of 50 Patients), Stratified by Presenting Vision.

	Baseline BCVA ≥20/200 (n = 25)				Baseline BCVA <20/200 (n = 25)			
Visual Acuity	Observation (n = 20)	Anti-VEGF IVI (n = 2)	PPV (n = 3)	*P* Value[a]	Observation (n = 13)	Anti-VEGF IVI (n = 3)	PPV (n = 9)	*P* Value[a]
Baseline: mean logMAR ± SD (Snellen)	0.36 ± 0.28 (20/45)	0.65 ± 0.50 (20/89)	0.47 ± 0.47 (20/59)	.439	1.94 ± 0.30 (20/1742)	2.10 ± 0.17 (20/2518)	2.24 ± 0.22 (20/3476)	.048
Final: mean logMAR ± SD (Snellen)	0.28 ± 0.24 (20/38)	0.14 ± 0.06 (20/27)	0.28 ± 0.17 (20/38)	.720	1.04 ± 0.82 (20/219)	0.80 ± 1.05 (20/126)	0.66 ± 0.54 (20/91)	.510
Change: mean logMAR ± SD	0.08 ± 0.17	0.51 ± 0.44	0.19 ± 0.30	.026	0.90 ± 0.80	1.30 ± 1.13	1.59 ± 0.45	.118

Abbreviations: ANOVA, analysis of variance; anti-VEGF, antivascular endothelial growth factor; BCVA, best-corrected visual acuity; IVI, intravitreal injections; PPV, pars plana vitrectomy; RAM, retinal arterial macroaneurysm; VA, visual acuity; VH, vitreous hemorrhage.
[a]One-way ANOVA test.

The final BCVA was similar between all treatment groups, and there was a significant difference in the mean change in vision from the baseline BCVA of 1.23 ± 0.89 (Snellen, 20/340) to the final BCVA of 0.54 ± 0.59 (Snellen 20/69) (−0.68 ± 0.78; $P < .001$) (Table 2). Most eyes showed a significant improvement in BCVA, but the IVI and PPV groups had worse presenting BCVA and greater visual improvements compared with the observation group (Table 3). Patients with a BCVA of ≥20/200 had a significantly higher vision change in the IVI and PPV groups (0.51 ± 0.44 and 0.19 ± 0.30, respectively) compared with the observation group (0.08 ± 0.17) ($P = .026$). Patients with a BCVA <20/200 had a significantly worse baseline BCVA in the IVI and PPV groups (2.10 ± 0.17 [Snellen 20/2518] and 2.24 ± 0.22 [Snellen 20/3476], respectively) compared with the observation group (1.94 ± 0.30, Snellen 20/1742) ($P = .048$).

There was no significant difference in age, sex, phakic lens status, final BCVA, and duration of follow-up in a combined analysis of all treatment groups (Table 2). There was no correlation between the number of injections and final BCVA ($r = 0.13$, $P = .830$). The IVI and PPV groups used significantly more anticoagulants than the observation group. However,

there was no significant difference in the final BCVA between patients using anticoagulant agents (0.52 ± 0.53 [Snellen 20/68]) compared with those who were not (0.55 ± 0.65 [Snellen 20/71]) ($P = .870$).

Conclusions

Rupture of RAMs can lead to contemporaneous VH and worse visual outcomes. Although many ruptured RAMs regress spontaneously, there is a risk for clinical complications, including visually significant VH, serous or rhegmatogenous retinal detachment, macular hole, and macular edema,[1] thus necessitating further intervention such as anti-VEGF IVI and PPV.

In our study, many patients with RAM and VH were older adults with a mean age of 75.5 years. There was no significant difference in patient age, sex, phakic lens status, or duration of follow-up between the 3 treatment groups. All eyes showed a significant improvement between the final and baseline BCVA in a combined analysis of all treatment groups (-0.68 ± 0.78, $P < .001$) (Table 2). In a stratified analysis, the IVI and PPV groups had worse presenting BCVA compared with the observation group, which may have influenced the physicians' choice of intervention.

When comparing the change in vision within each group, vision was improved in all patients. However, in the IVI group, the difference between initial and final BCVA did not reach statistical significance ($P = .068$), which may be due to the limited sample size. When comparing the vision change between groups, the PPV and IVI groups had a statistically significant greater improvement in vision compared with the observation group. This finding suggests that patients with worse presenting BCVA are more likely to receive IVI and PPV rather than observation; PPV may also allow a quicker return of vision. However, our study found that the final BCVA was similar between all treatment groups. This finding suggests that IVI and PPV had similar visual outcomes compared with the observation group despite being more invasive treatments.

Although patients with multiple treatments were excluded, our study found that IVI or PPV alone can be effective for VH resolution without the need for further intervention. Past studies have shown similar visual outcomes when using IVI and PPV for subretinal and macular hemorrhages secondary to exudative age-related macular degeneration or retinal macroaneurysm.[4,5] These findings suggest that IVI and PPV have similar clinical effectiveness in visual outcomes. There is likely not one best treatment of RAM with VH, and our results suggest that provider preference or a combination of both IVIs and PPV are reasonable treatment options.

Likewise, RAMs can be effectively treated by anti-VEGF agents. Our study found that anti-VEGF IVI had worse baseline BCVA but similar final BCVA compared with the observation group. This result suggests that anti-VEGF IVI has good visual outcomes, even in more severe cases.

In pathophysiology, RAMs can be caused by focal embolic damage to the arterial walls, leading to localized dilations along the retinal arterial branches. The resulting ischemia and hypoxia can trigger upregulated levels of VEGF, which can stimulate nitrogen oxide production in the endothelium, help activate the coagulation cascade, and increase vascular permeability.[6] Therefore, anti-VEGF agents such as bevacizumab, ranibizumab, and aflibercept can reduce nitrogen oxide production and cause vasoconstriction.

In recent years, anti-VEGF IVIs have been used to treat the exudation associated with RAM, including macular hemorrhage or edema.[6] Their vasoconstrictive effects can improve intraretinal exudation and macular edema, and their effects on the coagulation cascade and fibrinolysis can promote the dissipation of macular hemorrhage. Thus, IVI has been increasingly used to manage RAMs with or without VH.[6,7] Their vasoconstrictive effects can improve the localized dilations along the retinal arterial branches, while their activation of the coagulation cascade can manage any concomitant VH.

Several studies have shown the efficacy of anti-VEGF IVI toward improving visual outcomes.[7–9] In our study, the mean $\pm$ SD of injections was 3.6 ± 2.5 (range, 1-9). There was no correlation between the number of injections and the final BCVA ($r = 0.13$, $P = .830$), which suggests that the number of injections has a less important role in the treatment and improved visual outcomes of RAM with VH. This number of injections is in line with the induction phase commonly used for intravitreal anti-VEGF treatment.[10] This finding was also consistent with past literature, such as a study of 10 patients with RAM with macular exudation who were treated with either bevacizumab or ranibizumab as a first-line therapy.[9] The mean number of injections was 3.0 anti-VEGF IVI, and the final BCVA significantly improved. In a different study, 23 patients with symptomatic RAM with macular exudation or hemorrhage were treated with bevacizumab only as first-line therapy.[8] The mean $\pm$ SD of injections for the treated group was 1.42 ± 0.69, and final BCVA improved within 3 months ($P = .010$). Although the number of injections can vary, multiple studies have shown a significant improvement in the final VA and suggest that the number of injections has a less contributing role in visual outcomes.[3,8,9,11]

PPV is a surgical treatment option more invasive than IVI, particularly in the older adult population.[12–14] In the cases of RAM with VH, PPV enhances visualization of the underlying pathology for observation or to allow for other treatment options including laser to the RAM. Additionally, PPV can remove preretinal blood to promote a faster recovery and prevent the formation of epiretinal membrane with risk for retinal tissue damage.[1] Several studies have shown that PPV is an effective treatment method to address more complicated, severe cases of RAM with VH.[1,15] In our study, the mean $\pm$ SD time to intervention was 13 ± 15.3 days for PPV and 38 ± 69.9 days for IVI. One hypothesis is that PPV is more often recommended for moderate to severe cases with the need for a sooner return of higher level of visual acuity or prompter need to clear an obscuring VH to properly monitor the RAM in subsequent months. Thus, patients will undergo a PPV earlier compared with their first IVI injection, suggesting the hemorrhage may be too dense to clear with IVI alone.

In addition, provider preference may play a larger role in the treatment modality rather than the superiority of one treatment over another. In our study, patients with a BCVA of ≥20/200 had a significantly higher vision change in the IVI and PPV groups compared with the observation group. There was no significant difference in the baseline and final BCVA among the treatment groups. This finding suggests that patients with a BCVA ≥20/200 have similar final visual outcomes regardless of the treatment arm.

Likewise, patients with a BCVA <20/200 had significantly worse baseline BCVA in the IVI and PPV groups compared with the observation group. There was no significant difference in the final BCVA and vision change among the treatment groups. This finding suggests that patients with a BCVA <20/200 have similar final visual outcomes regardless of the treatment arm, but providers may opt to choose IVI or PPV for patients with worse presenting vision. Likewise, providers may choose observation alone for patients with better presenting vision because they would have excellent vision outcomes without the need for more invasive treatments. Our study suggests that VH in the setting of RAM may have little bearing on the final BCVA, which is usually significantly improved from baseline.

Antiplatelet and anticoagulant usage has been associated with several types of intraocular bleeds, including vitreous and subretinal hemorrhages.[16–19] Our study found that the IVI and PPV groups used significantly more anticoagulants than the observation group. This finding suggests that patients on antiplatelets and/or anticoagulants were more likely to experience RAM with VH and may need further interventions rather than observation alone. However, there was no significant difference in the final BCVA between patients using anticoagulant agents (0.52 ± 0.53 [Snellen 20/68]) compared with those who were not (0.55 ± 0.65 [Snellen 20/71]) ($P = .870$). This finding suggests that patients on anticoagulants were more likely to receive IVI or PPV but still have visual outcomes similar to those of patients not on anticoagulants without the need for IVI or PPV.

One hypothesis is that anticoagulant use or type may have a less important role in the development of RAM with VH and in turn may not necessitate the need for IVI or PPV if visual outcomes remain the same. Anecdotally, vitreoretinal specialists may choose less invasive methods such as IVIs over incisional surgery in patients on anticoagulants. Likewise, these providers may be more apt to treat a patient with VH on anticoagulants due to the perception that bleeding is worse and less likely to clear in these patients.

In our study, patients on anticoagulants continued their blood thinners throughout the treatment. Of patients who had a decline in final BCVA, none had secondary bleeding complications with their treatment. This finding suggests that although anticoagulation is associated with worse presenting BCVA, it is not associated with secondary bleeding complications throughout the course of treatment or final BCVA outcomes. Similarly, past studies have found that anticoagulants have a lesser role in the risk for intraocular hemorrhage.[20,21] However, other studies have found a higher association between anticoagulant use or type and intraocular hemorrhage.[17,22] Thus, future studies are needed to characterize the association between anticoagulant use or type and incidence of VH in RAM.

One complication of RAM is the development of subretinal hemorrhages. This type of bleed has a more guarded prognosis due to the irreversible functional and anatomic damage to the photoreceptor layer, particularly if located in the macula. Subretinal tPA may be used to dissolve subretinal clots and minimize photoreceptor damage on the retina.[23] In our study, the incidence of subretinal hemorrhage was 18.2% in the observation group, 25.0% in the surgery group of which 8.3% had treatment with subretinal tPA, and 60.0% in the IVI group. Small subretinal hemorrhages can be self-limited or treated with anti-VEGF monotherapy or IVI of intraocular gas (such as perfluoropropane) with or without tPA.[24] Larger, thicker, and subfoveal subretinal hemorrhages may warrant consideration of PPV with subretinal injections of tPA.[24]

In our study, all incidences of subretinal hemorrhage were present at baseline. The higher rate of subretinal hemorrhages in the IVI group may be attributed to the smaller sample, and further studies are needed to determine the association between IVI and subretinal hemorrhages. If present, any submacular heme involving the fovea can worsen BCVA regardless of the treatment options and make it difficult to gauge the clinical effectiveness of IVI. However, some studies have shown a higher risk for subretinal hemorrhages after an anti-VEGF IVI in a number of ocular conditions.[25–28] Anti-VEGF IVI can increase the risk for pigment epithelial tears and detachment, leading to hemorrhages underneath the retinal epithelium. However, other studies have used anti-VEGF agents as an adjuvant treatment of subretinal hemorrhage.[8,29] Thus, the association between anti-VEGF IVI and subretinal hemorrhages has varied results and needs to be further elucidated in future studies.

One limitation of our study is the small sample size of the study groups and its retrospective nature, which limited the statistical power of the study. The study also involved patients from multiple providers in the same institution, and we could not account for provider differences or preferences in the treatment and management of RAM with VH. Although a classic treatment of RAM, the focal laser was not considered in this study because it was not possible to effectively deliver laser due to the underlying VH. In addition, the study's focus was on the effects of PPV or IVI separately compared with that of observation. However, the same patient in the real-world population may have multiple different treatments performed. For our study, we excluded eyes with multiple treatments to compare different treatment groups without overlapping interventions and to have homogenous groups and limit bias. Likewise, there is a period of observation between diagnosis and intervention (PPV or IVI). There is a possibility of observation bias because this period may have allowed clearance of the blood and changed a potential patient undergoing PPV or IVI into a patient undergoing observation.

Future studies, perhaps those using prospective cohorts or multicenter trials, could focus on the recruitment of more patients to increase sample size and statistical power, although

this could be challenging in an older population with multiple medical comorbidities. Potential studies could also incorporate other treatment modalities, including focal laser, pneumatic diplacement of subretinal hemorrhage, or other therapies. Another study could include patients with multiple treatments to identify clinical outcomes of combined treatment groups such as IVI and PPV.

In conclusion, we investigated the clinical outcomes of RAMs with VH managed with observation, anti-VEGF IVI, or PPV. Patients with RAM and VH are typically older adults, and all treatment groups in our study demonstrated similar final visual outcomes and significantly improved BCVA from baseline. The IVI (40%) and PPV (76.9%) arms were more frequently on anticoagulants ($P = .011$). Improved BCVA was not impacted by the number of injections or anticoagulant use, suggesting that these factors may play a less important role in the treatment of RAM with VH.

Authors' Note

Dr. Klufas is also affiliated with Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA.

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Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information was performed in a US Health Insurance Portability and Accountability Act–compliant manner. This study was approved by the Institutional Review Board of Wills Eye Hospital, and a waiver for informed consent was obtained due to the retrospective nature of this study.

Statement of Informed Consent

Informed consent was obtained prior to performing the procedure or surgery. Consent to publish this case series was not obtained. This report does not contain any personal information that could lead to the identification of the studied patients.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Klufas is a consultant to Genentech, Allergan, Alimera and RegenexBio, and a speaker for Regeneron, Genentech, Biogen, and Coherus. None of the other authors declared conflicts of interest.

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ORCID iDs

Sophia S. Lam https://orcid.org/0000-0002-5213-0902

Abtin Shahlaee https://orcid.org/0000-0001-7980-9109

References

1. Speilburg AM, Klemencic SA. Ruptured retinal arterial macroaneurysm: diagnosis and management. *J Optom*. 2014;7(3):131-137.
2. Wilkins CS, Mehta N, Wu CY, Barash A, Deobhakta AA, Rosen RB. Outcomes of pars plana vitrectomy with subretinal tissue plasminogen activator injection and pneumatic displacement of fovea-involving submacular haemorrhage. *BMJ Open Ophthalmol*. 2020;5(1):e000394.
3. Cho WH, Chiang WY, Chen CH, Kuo HK. To treat or not to treat: a clinical series of retinal arterial macroaneurysms: a single-center retrospective study. *Medicine (Baltimore)*. 2020;99(5):e19077.
4. Herranz Cabarcos A, Quiroz Quiroga MJ, Alarcon Valero I, Castilla Marti M, Pospoki V, Vilaplana Blanch D. Vitrectomy with subretinal tissue plasminogen activator (r-TPA) and intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) for submacular hemorrhages treatment: retrospective analysis of 22 cases. *Arch Soc Esp Oftalmol (Engl Ed)*. 2022;97(7):391-395.
5. Tiosano A, Gal-Or O, Fradkin M, et al. Visual acuity outcome in patients with subretinal hemorrhage - office procedure vs. surgical treatment. *Eur J Ophthalmol*. 2023;33(1):506-513.
6. Lin Z, Hu Q, Wu Y, Xu J, Zhang Q. Intravitreal ranibizumab or conbercept for retinal arterial macroaneurysm: a case series. *BMC Ophthalmol*. 2019;19(1):18.
7. Pichi F, Nucci P, Ciardella AP. Intravitreal bevacizumab for macular complications from retinal arterial macroaneurysms. Reply. *Am J Ophthalmol*. 2013;155(4):774-775.
8. Cho HJ, Rhee TK, Kim HS, et al. Intravitreal bevacizumab for symptomatic retinal arterial macroaneurysm. *Am J Ophthalmol*. 2013;155(5):898-904.
9. Zweifel SA, Tonz MS, Pfenninger L, Becker M, Michels S. Intravitreal anti-VEGF therapy for retinal macroaneurysm. *Klin Monbl Augenheilkd*. 2013;230(4):392-395.
10. Brown DM, Regillo CD. Anti-VEGF agents in the treatment of neovascular age-related macular degeneration: applying clinical trial results to the treatment of everyday patients. *Am J Ophthalmol*. 2007;144(4):627-637.
11. Scott IU, VanVeldhuisen PC, Ip MS, et al. Effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion: the SCORE2 randomized clinical trial. *JAMA*. 2017;317(20):2072-2087.
12. Omari A, Mahmoud TH. Vitrectomy. In: *StatPearls*. StatPearls Publishing; 2022.
13. Choovuthayakorn J, Khunsongkiet P, Patikulsila D, et al. Characteristics and outcomes of pars plana vitrectomy for proliferative diabetic retinopathy patients in a limited resource tertiary center over an eight-year period. *J Ophthalmol*. 2019;2019:9481902.
14. El Annan J, Carvounis PE. Current management of vitreous hemorrhage due to proliferative diabetic retinopathy. *Int Ophthalmol Clin*. 2014;54(2):141-153.
15. Asao K, Nakada A, Kawasaki Y. Vitreous hemorrhage caused by ruptured retinal macroaneurysm. *Case Rep Ophthalmol*. 2014;5(1):44-49.

16. Kiernan DF, Hariprasad SM, Rusu IM, Mehta SV, Mieler WF, Jager RD. Epidemiology of the association between anticoagulants and intraocular hemorrhage in patients with neovascular age-related macular degeneration. *Retina*. 2010;30(10):1573-1578.
17. Talany G, Guo M, Etminan M. Risk of intraocular hemorrhage with new oral anticoagulants. *Eye (Lond)*. 2017;31(4):628-631.
18. Starr MR, Ammar MJ, Patel LG, et al. Comparative incidence of postoperative hemorrhage in vitreoretinal surgery in patients on anti-coagulants. *Ophthalmic Surg Lasers Imaging Retina*. 2021; 52(7):374-379.
19. Shieh WS, Sridhar J, Hong BK, et al. Ophthalmic complications associated with direct oral anticoagulant medications. *Semin Ophthalmol*. 2017;32(5):614-619.
20. Caldeira D, Canastro M, Barra M, et al. Risk of substantial intraocular bleeding with novel oral anticoagulants: systematic review and meta-analysis. *JAMA Ophthalmol*. 2015;133(7): 834-839.
21. Sun MT, Wood MK, Chan W, et al. Risk of intraocular bleeding with novel oral anticoagulants compared with warfarin: a systematic review and meta-analysis. *JAMA Ophthalmol*. 2017; 135(8):864-870.
22. Shin YI, Sung JY, Sagong M, Lee YH, Jo YJ, Kim JY. Risk factors for breakthrough vitreous hemorrhage after intravitreal anti-VEGF injection in age-related macular degeneration with submacular hemorrhage. *Sci Rep*. 2018;8(1):10560.
23. Singh RP, Patel C, Sears JE. Management of subretinal macular haemorrhage by direct administration of tissue plasminogen activator. *Br J Ophthalmol*. 2006;90(4):429-431.
24. Novelli FJD, Preti RC, Monteiro MLR, Nobrega MJ, Takahashi WY. A new method of subretinal injection of tissue plasminogen activator and air in patients with submacular hemorrhage. *Retina*. 2017;37(8):1607-1611.
25. Baeteman C, Hoffart L, Galland F, Ridings B, Conrath J. Subretinal hemorrhage after intravitreal injection of anti-VEGF for age-related macular degeneration: a retrospective study. *J Fr Ophtalmol*. 2009;32(5):309-313. French
26. Karagiannis DA, Ladas ID, Parikakis E, et al. Changing from bevacizumab to ranibizumab in age-related macular degeneration. Is it safe? *Clin Interv Aging*. 2009;4:457-461.
27. Modarres M, Naseripour M, Falavarjani KG, Nikeghbali A, Hashemi M, Parvaresh MM. Intravitreal injection of 2.5 mg versus 1.25 mg bevacizumab (Avastin) for treatment of CNV associated with AMD. *Retina*. 2009;29(3):319-324.
28. Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. *Eye (Lond)*. 2013;27(7):787-794.
29. Jeong S, Park DG, Sagong M. Management of a submacular hemorrhage secondary to age-related macular degeneration: a comparison of three treatment modalities. *J Clin Med*. 2020; 9(10):3088.