Intravitreal bevacizumab monotherapy for large and thick submacular hemorrhage (SMH) of less than one week duration secondary to neovascular AMD

Kamal Kishore, MD[1]; Sachin Jain, BS; Chirag V Patel, MD[2]

1. Assistant Clinical Professor UIC-Peoria, IL 2. Carle Clinic, Urbana, IL

Introduction

The natural history of SMH secondary to neovascular age-related macular degeneration (N-AMD) results in a poor anatomical and visual outcome in most patients.[1,2,3] Such patients are usually not eligible for thermal laser or photodynamic therapy, and were excluded from the pivotal trials that led to the FDA approval of ranibizumab. Several treatment options such as pneumatic displacement of blood with[4] or without intravitreal tissue plasminogen activator (TPA),[5] surgical removal of hematoma with[6,7] or without[8] removal of underlying choroidal neovascular membrane (CNVM), vitrectomy with subretinal injection of TPA for pneumatic displacement of blood[7] have been proposed with variable results. Excision of CNVM with removal of blood as performed in Submacular Surgery Trial (SST) did not improve visual outcome compared to natural history.[6] Surgical approaches are generally recommended for patients with thick hemorrhage, defined as those with visible elevation of the retina, partly because of the belief that thick hemorrhages are more likely to result in a disciform scar due to organization of the blood clot.[9]

Anti-VEGF monotherapy, either alone or in combination with other treatment modalities has been evaluated in several small-scale retrospective studies with encouraging results.[10,11] None of them specifically studied patients with large and thick SMH of recent duration.

Berrocal et al[1] noted that patients with SMH not associated with a CNVM had an excellent outcome without treatment, with most patients regaining visual acuity of 20/40 or better regardless of the size or thickness of the hemorrhage. We have previously noted disciform scar formation in patients with SMH secondary to AMD where anti-VEGF monotherapy was initiated two weeks or later after the onset of hemorrhage. We therefore reviewed charts of patients with large (2 disk areas or more) and thick SMH of less than one week duration treated with anti-VEGF monotherapy to evaluate whether prompt control of neovascular process might lead to prevention of disciform scar and improve visual acuity.

Methods

Retrospective chart review of ten eyes of ten patients presenting with an acute decrease in vision secondary to thick SMH from N-AMD from September 2006 through December 2009. Those with < 6 months of follow up, symptoms of > 7 days duration, pre-existing disciform scar, vision worse than 20/400 prior to the occurrence of SMH, absence of blood beneath the fovea, or recent (<3 months) MI or stroke were excluded. Complete eye examination, FA and OCT were performed at presentation. Lesion size was measured using OIS WinStation™ software (Ophthalmic Imaging Systems, Sacramento, CA). Snellen acuity was converted into logMAR for statistical analysis, which was performed using Microsoft Excel® (Microsoft Corporation, Redmond, Washington). Visual acuity of counting fingers and hand motions were assigned logMAR value of 1.6 and 2.0 respectively.[12] Monthly intravitral injections of 1.25 mg bevacizumab (0.05mL) were given until resolution of SMH and less frequently thereafter, primarily based on clinical examination and spectral domain OCT.

Financial Disclosures: None

Contact Information: kishorekvn@comcast.net

Results

Ten eyes of 10 patients (M=2, F=8, mean age 82.6, range 70-89 years) were analyzed. Four had previously been treated for N-AMD; three with intravitreal bevacizumab 18, 20 and 20 weeks prior to the onset of SMH, and the fourth with thermal laser ten years ago. SMH was the first manifestation of N-AMD in the remaining 6 patients. Seven of 10 patients were on aspirin, and one on aspirin and dipyridamole. Patients presented after a median of 4 (Mean 4.2, range 2-7) days after the onset of acute central scotoma. Mean lesion size was 28.4±28.81(range 5.4-100, median 14.21) mm^2 , with blood comprising 80-95% of the lesion. Presenting VA ranged from 20/60 to HM (mean 20/400). Patients received a mean of 7.7 (range 5-13) injections over a mean FU of 13.2 (range 6-41) months. Final VA ranged from 20/40 – 20/400, mean 20/100, improved in 9 eyes, and was unchanged in one which had previously been treated with foveal thermal laser **(Table, Figure 1 and 2).** Mean change in visual acuity was -0.7±0.55 logMAR (p=0.0047, paired t-test). FA after resolution of SMH showed an occult CNVM in 8 eyes, and regressed classic and peripapillary CNVM in one eye each. A thin subretinal scar was noted in two eyes, and no scar in the remaining 8. SDOCT showed a dry macula in all eyes at final follow up.

Table: Patient Information

Patient	Age/Sex	Duration of symptoms (days)	Lesion size (mm^2)	Initial Snellen VA	Final Snellen VA	Final Appearance of fovea	Number of injections	Follow-Up (months)
1	72/F	7	46.08	20/80	20/50	No scar	9	41
2	86/F	4	100	HM	20/50	No scar	7	7
3	82/F	7	13.38	20/200	20/80	Thin scar	13	20
4	89/M	2	5.4	CF 3ft	20/70	No scar	6	8
5	74/F	2	9.12	HM	20/200	No scar	5	6
6	89/M	7	11.86	20/200	20/50	No scar	10	15
7	87/F	2	15.04	20/60	20/50	No scar	9	12
8	89/F	2	33.29	20/400	20/400	laser scar	8	11
9	88/F	6	10.79	CF3ft	20/40	No scar	5	6
10	70/F	3	39.38	CF4ft	20/400	Thin scar	5	6

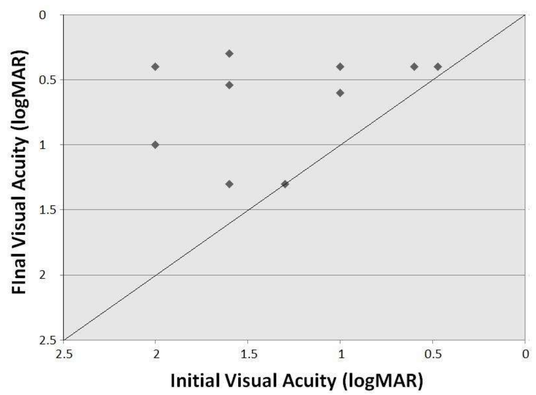


Figure 1

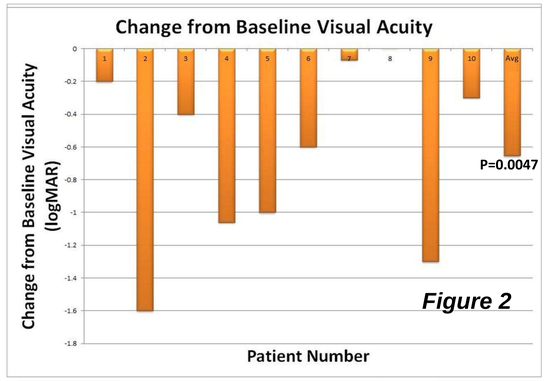
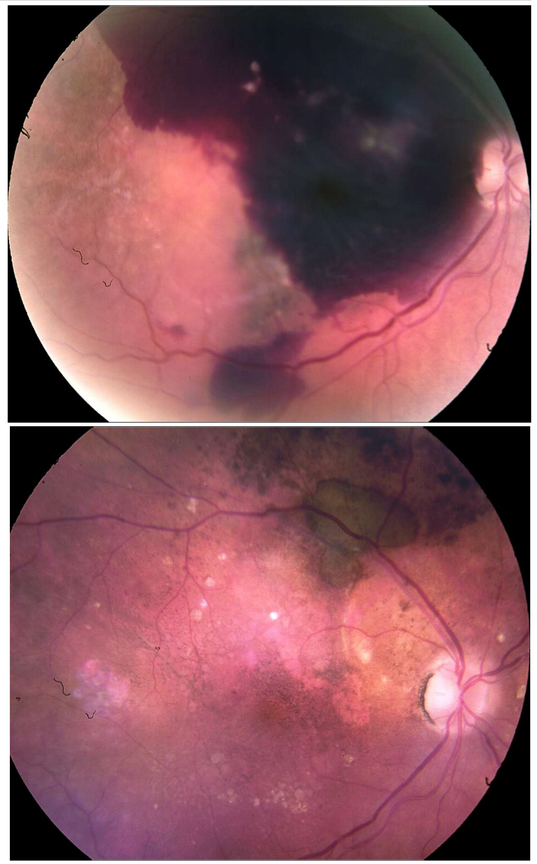


Figure 2



Patient #2: At Presentation (Top) and Seven Months Later (Bottom)

Discussion

Anti-VEGF monotherapy has revolutionized the management of N-AMD. However, its role in the management of predominantly hemorrhagic lesions is not well established. Subretinal blood may act as diffusion barrier, can cause iron toxicity, and damage photoreceptors by clot retraction. Thus, several therapeutic interventions have been tried to remove or displace subretinal blood with variable outcomes. However, TPA does not penetrate the retina,[13] pneumatic displacement may cause shearing injury to photoreceptors, and procedures involving vitrectomy subject the patients to additional risks such as retinal detachment.[6]

Encouraging results have been reported with anti-VEGF monotherapy in patients with SMH due to N-AMD. Stifter et al[10] demonstrated that of 21 eyes with SMH secondary to N-AMD that were treated with intreavitreal bevacizumab, 48% had improvement in VA, 9.5% demonstrated no change, while 43% had a decrease in VA at 4 months. However, patients without subfoveal hemorrhage were included, thickness of hemorrhage was not specified, and 7 (33%) had SMH >30 days duration prior to treatment.

Our study has shown that disciform scar formation can be prevented if anti-VEGF monotherapy is initiated within one week from the onset of SMH. Gehrs et al[9] showed that organization of blood clot is a major component of disciform scar. However, no disciform scar forms in patients where etiology of SMH is other than a CNVM.[1] Thus, vascular proliferation is needed for scar formation, and its inhibition by early anti-VEGF monotherapy may prevent scarring. We have previously noted scar formation in patients where anti-VEGF monotherapy was instituted two weeks or later from the onset of SMH.

Hemorrhage resolved in all patients within six months with improvement in vision in all except one eye that had previously been treated with foveal thermal laser. Mean visual acuity improved from 20/400 at baseline to 20/100 at final follow-up. Most (80%) patients were noted to have occult CNVM, as has been shown previously.[14]

Anti-VEGF monotherapy, if initiated early, appears to be safe and effective in the management of predominantly hemorrhagic N-AMD lesions.

Bibliography

1. Berrocal MH, Lewis ML, Flynn HW Jr. Variations in the clinical course of submacular hemorrhage. Am J Ophthalmol. 1996;122:486–493.
2. Avery RL, Fekrat S, Hawkins BS, et al. Natural history of subfoveal subretinal hemorrhage in age-related macular degeneration. Retina. 1996;16:183–189.
3. Bennet SR, Folk JC, Blodi CF, et al. Factors prognostic of visual outcome in patients with subretinal hemorrhage. Am J Ophthalmol. 1990;109:33–37.
4. Hassan AS, Johnson MW, Schneiderman TE, et al. Management of submacular hemorrhage with intravitreous tissue plasminogen activator injection and pneumatic displacement. Ophthalmology. 1999;106:1900–1907.
5. Ohji M, Saito Y, Hayashi A, Lewis JM, Tano Y. Pneumatic displacement of subretinal hemorrhage without tissue plasminogen activator. Arch Ophthalmol. 1998;116:1326–1332.
6. Bressler NM, Bressler SB, Childs AL, et al. Submacular Surgery Trials (SST) Research Group: surgery for hemorrhagic choroidal neovascular lesions of age-related macular degeneration: ophthalmic findings: SSTreport no. 13. Ophthalmology. 2004;111:1993–2006.
7. Thompson JT, Sjaarda RN. Vitrectomy for the treatment of submacular hemorrhages from macular degeneration: A comparison of submacular hemorrhage/membrane removal and submacular tissue plasminogen activator-assisted pneumatic displacement. Trans Am Ophthalmol Soc. 2005;103:98–107.
8. Wade EC, Flynn HW Jr, Olsen KR, et al. Subretinal hemorrhage management by pars plana vitrectomy and internal drainage. Arch Ophthalmol. 1990;109:973–978.
9. Gehrs KM, Heriot WJ, de Juan E Jr. Transmission electron microscopic study of a subretinal choroidal neovascular membrane due to age-related macular degeneration. Arch Ophthalmol. 1992;110:833-7.
10. Stifter E, Michels S, Prager F, et al. Intravitreal bevacizumab therapy for neovascular age-related macular degeneration with large submacular hemorrhage. Am J Ophthalmol. 2007;144(6):886–892.
11. Chawla S, Misra V, Khemcandani M. Pneumatic displacement and intravitreal bevacizumab: A new approach for management of submacular hemorrhage in choroidal neovascular membrane. Indian J Ophthalmol. 2009;57:155–7.
12. Arroyo JG, Postel EA, Stone T, *et al.* A matched study of primary scleral buckle placement during repair of posterior segment open globe injuries. Br J Ophthalmol 2003;87:75–8.
13. Kamei M, Misono K, Lewis H. A study of the ability of tissue plasminogen activator to diffuse into the subretinal space after intravitreal injection in rabbits. Am J Ophthalmol. 1999;128(6):739–746.
14. Grossniklaus HE, et al. Histopathologic and ultrastructural features of surgically excised subfoveal choroidal neovascular lesions: submacular surgery trials report no. 7. Arch Ophthalmol. 2005;123:914–921.