Local and systemic complications after intravitreal administration of anti-vascular endothelial growth factor agents in the treatment of different ocular diseases: A five-year retrospective study

CATEGORY: Original Article – Clinical Science

LOCAL AND SYSTEMIC COMPLICATIONS AFTER INTRAVITREAL ADMINISTRATION OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS IN THE TREATMENT OF DIFFERENT OCULAR DISEASES: A 5-YEAR RETROSPECTIVE STUDY

Raffaele NUZZI PhD, Federico TRIDICO MD

INSTITUTE ADDRESS:

Institute of Ophthalmology, Department of Clinical Pathophysiology - Visual System and Eye Clinic Section - University of Turin, Via Juvarra 19, 10100 Turin, Italy

CORRESPONDING AUTHOR:

R. Nuzzi, Institute of Ophthalmology, Department of Clinical Pathophysiology – Visual System and Eye Clinic Section – University of Turin, via Juvarra 19, 10100, Turin, Italy.
E-mail: prof.nuzzi_raffaele@hotmail.it

RUNNING TITLE: Complications after Anti-VEGF drugs

CONFLICT OF INTERESTS STATEMENT: The Authors declare that there is no existing/potential conflict of interest.

FINANCIAL DISCLOSURE: None.

ABSTRACT

Background: The main purpose of this study is to assess the frequency of local and systemic complication in patients undergoing intravitreal bevacizumab, ranibizumab and/or pegaptanib for the treatment of different ocular diseases.

Design: Retrospective cohort study.

Methods: Charts of patients who received treatment with anti-Vascular Endothelial Growth Factor (VEGF) from June 2007 to December 2011 were retrospectively reviewed. Out of 1117 eyes, 732 were treated with bevacizumab, 356 with ranibizumab and 29 with pegaptanib. Data recorded included demographic information, clinical findigs, total number of anti-VEGF injection received, and appearance of both ocular and systemic complications according to the judgment of single physicians. Increases above baseline of intraocular pressure (IOP) were considered significant if >5 mmHg on ≥2 consecutive follow-up visits.

Main Outcome Measures: The frequency and odds ratio of side-effects were compared between patients treated with bevacizumab, ranibizumab and pegaptanib. Complication type, anti-VEGF drug, and primary ocular disease rates in eyes affected by adverse events were also recorded.

Results: 9.02% of the eyes treated with bevacizumab presented side-effects, while ratings in the ranibizumab and pegaptanib groups were respectively 9.83% and 20%. Odds ratios calculated comparing incidences after each anti-VEGF are 0.91 (bevacizumab versus ranibizumab group, p=0.664), 0.38 (bevacizumab versus pegaptanib, p=0.042) and 0.42 (ranibizumab versus pegaptanib, p=0.076). A total of 117 complications were detected. Ocular side effects registered were 20 sustained IOP elevation (10 after bevacizumab, 9 after ranibizumab and 1 after pegaptanib), 1 infectious uveitis, 1 tractional retinal detachment and 1 sub-retinal hemorrhage after bevacizumab injection; mostly occurred in patients affected by Age-related Macular Degeneration (AMD). Other cases were related to transient IOP elevation immediately after injection. Systemic complication registered were one case of nausea and uneasiness plus one episode of chest pain with acute vision loss in both eyes after bevacizumab injection; and one episode of acute blood hypertension after pegaptanib.

Conclusions: The majority of significant adverse effects occurred in patients that received multiple bevacizumab administrations. However results may be affected by the difference in the utilization amount for each anti-VEGF drug. AMD patients were the most represented probably due the greater indication to treatment.

KEY WORDS: Anti-VEGF –Bevacizumab – Ranibizumab – Pegaptanib – Adverse effects

INTRODUCTUION

Intravitreal anti-Vascular Endothelial Growth Factor (VEGF) agents usage is widely spread as primary treatment of many vitreo-retinal disease such as neovascular age-related macular degeneration, diabetic macular edema, macular edema secondary to retinal vein occlusion and other conditions. The drugs included in this class are currently represented by bevacizumab, ranibizumab (Avastin and Lucentis, respectively; Genentech, South San Francisco, CA) and pegaptanib (Macugen; OSI-Eyetech, New York, New York, USA).

Information about the safety of ranibizumab and pegaptanib comes from several large-scale randomized clinical trials evaluating their utilization in patients with choroidal neovascularization secondary to AMD[1,2,3]. These studies concluded that complications from these injections are extremely rare, if the procedure is conducted with proper precautions. As today, not enough trials involving Bevacizumab have been planned implying lack of strong, prospective evidence supporting the safety of intravitreal administration[4]. Additional assessments about adverse effects (ocular or systemic) are reported in recent retrorospective case-series[5,6].

With respect to bevacizumab, major ocular complications associated with treatment are severe uveitis[7], tractional retinal detachment[8], intraocular pression (IOP) elevation[9,10,11] and ocular hemorrhage[12]. Detailed safety data reports for ranibizumab injection in the treatment of neovascular AMD (ANCHOR and MARINA) showed important association with ocular inflammation (prevalence range 1-2%). Other reports referred episodes of ocular hemorrhage following ranibizumab[13,14]. In trials evaluating continuous injection of pegaptanib, no ocular safety problems have been found (most complications were attributed to injection procedure)[15].

Also, rare systemic adverse reactions have been associated with intravitreal injection of anti-VEGF. The overall incidence of systemic adverse events in the ranibizumab trials was low, but the apparent increase in nonocular hemorrhages and thromboembolic events suggested potential increased risks with ranibizumab treatment. During the 3 years of experience with pegaptanib in the VISION trials no systemic safety concerns have emerged in subjects receiving pegaptanib. The most common nonocular adverse events were infections (18%), respiratory (15%) and gastrointestinal disorders (14%). An increase in blood pressure was the most common systemic side effect associated with bevacizumab injections, followed by cerebrovascular accidents (0.21%) and myocardial infarction. Rate of cardiovascular events was low and not always attributable to the drug itself[16,17].

Given the growing importance of anti-VEGF factors in the management of various ocular diseases, a closer look at their potential side-effects is advisable. Furthermore the majority of clinical trials assessing the handling of these medications are focused on their utilization in the treatment of AMD; therefore detailed information about their usage in other ocular pathologies is still incomplete.

The purpose of this article is to present our 5-year report of complications (both ocular and systemic) following intravitreal administration of bevacizumab, ranibizumab and pegaptanib, as well as evaluate our safety experience for each drug in the treatment of AMD, diabetic macular edema (DME) and edema secondary to retinal veins thrombosis or macular myopic disease.

METHODS

This study is a retrospective clinical chart review, for which were analyzed charts of patients who arrived at our Macular Disease Centre to be visited and underwent treatment with bevacizumab, ranibizumab or pegaptanib intravitreal injections performed from June 2007 to December 2011.

The following data was recorded from each chart: age and sex of the patient, clinical history of hypertension, diabetes or other relevant systemic condition, personal history of glaucoma, main ocular

disease (which deserved anti-VEGF treatment), previous cataract surgery, what anti-VEGF was used (and if more than a single drug was administered during the treatment cycle), post-operatory IOP, the number of total injections performed and in which injection occurred the adverse effect.

A total of 1117 eyes recieved anti-VEGF agents (732 treated with bevacizumab, 356 with ranibizumab, 29 with pegaptanib). 107 eyes presenting adverse effects were identified. Table 1 shows the demographic characteristics of the population of interest. Registered adverse events following anti-VEGF injection were considered related to the drug according to the judgment of single ophthalmologists or internal medicine specialists who examined the patients during the regular follow-up visit or at the time of the event presentation. In general were taken into account side effects occurred within two weeks after injection. About the assessment of sustainable IOP elevation, changes from baseline >5 mmHg registered in two consecutive follow-up visits after the injection were considered significant. The observed eyes have been divided in groups according to the mainly used anti-VEGF, in order to compare safety features for each drug.

RESULTS

Of the eyes treated with bevacizumab, 9.02% presented side-effects (66 eyes out of 732), while ratings in the ranibizumab and pegaptanib groups are respectively 9.83% (35 out of 356) and 20% (6 out of 29). The difference in incidence between bevacizumab and ranibizumab group was not statistically significant ($p=0.664$) with an odds ratio of 0.91. On the contrary, odds ratio found confronting bevacizumab and pegaptanib was 0.38 ($p=0.042$), while the one calculated by comparing ranibizumab with pegaptanib sub-group was 0.42 ($p=0.076$). 117 adverse events were registered: 73 occurred after injection of bevacizumab (63.79%), 38 after ranibizumab (31.03%) and 6 after pegaptanib (5.17%). Table 2 reports a summary of the side-effects divided by anti-VEGF used while table 3 shows the relationship between eyes with complications and primary ocular disease after bevacizumab, ranibizumab and pegaptanib injections.

As of local complications, there were 20 cases of sustained IOP elevation (overall prevalence 1.79%), 1 sub-retinal hemorrhage (0.08%), 1 retinal detachment (0.08%) and 1 infectious uveitis (0.08%). The 69.57% of these events occurred in patients affected by AMD, while the uveitis involved an eye with DME. Remaining events refer to transient IOP elevation registered immediately after the operation (overall prevalence 8,15%) with patients classified in three groups according to total number of injection received (Table 4). All anti-VEGF agents were related with sustained IOP elevation in 2 or more consecutive visits, occurred mostly at the time of second injections (35% of ocular hypertension cases). 10 patients with diagnosis of IOP elevation suffered a previous episode immediately after the injection. Treatment was not suspended after diagnosis, besides 5 patient were administered different anti-VEGF afterwards without significant changes in IOP. Data regarding eyes involved, number of injections received and related primary ocular disease are shown in tabes 5 (bevacizumab group), 6 (ranibizumab group) and 7 (pegaptanib). Intraocular hemorrhage, tractional retinal detachment, and severe uveitis occurred after administration of bevacizumab. Retinal detachment and hemorrhage happened at the time of the first injection, while infectious uveitis occurred after the third injection (table 8), inducing immediate treatment interruption.

On the other hand, three post-operative systemic complications were discovered. Nausea, general uneasiness and chest pain with acute vision loss in both eyes happened after administration of bevacizumab, though following ECG was negative for myocardial infarction. A single episode of acute blood hypertension, with systolic pression values >200 mmHg, was observed after second injection of intravitreal pegaptanib. All systemic adverse events occurred in eyes affected with AMD (Table 9).

DISCUSSION

Significant adverse effects were infrequent, with transient post-operatory IOP elevation as most detected ocular complication. However it was difficult to assess if such complication was actually related to anti-VEGF therapy, since the majority of events occurred in eyes who received less than six injection with a large portion detected at the time of the first injection. Clinical chart analysis indicates that additional injections did not seemed to be strongly related to the incidence of such adverse effect. Moreover ocular hypertension was transient and returned to baseline values after instillation of anti-glaucoma drops immediately after IOP measurement, and remained mostly stable during follow-up. Therefore post-operative IOP elevation may be related to injection procedure itself rather than use of anti-VEGF and so may interfere with the effective. On the contrary, we observed a significant correlation between anti-VEGFs and developing of sustainable IOP elevation, especially after multiple bevacizumab and ranibizumab injections.

The majority of ocular and systemic adverse effects registered in the study population seemed to involve patients affected with AMD that received bevacizumab. This can be explained with the larger indication dedicated to the disease. However eyes with diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion and macular myopic disease were often related to ocular adverse manifestations after injections with bevacizumab, too. Moreover side-effects were detected mostly in eyes who underwent 3 or more total injections (especially at the time of second injection) reflecting increasing rates with the length of treatment. Finally, pegaptanib injections were related to less complications compared with other anti-VEGF and no systemic events were identified after ranibizumab treatment.

This 5-year findings suggest that bevacizumab treatment leads to side-effects with greater frequency than other anti-VEGF agents, however results may be affected by his greater utilization, with its consolidated efficacy and lower costs if compared with ranibizumab with no difference in efficacy[18]. For this reasons, this anti-VEGF remains widely used in the treatment of coroidal neovascularization related conditions. Similar conclusions can be applied to adverse events related to pegaptanib, because of its currently limited use that may possibly alter the effective incidence of adverse effects.

Even though complications are rare, they should not be overlooked, given the importance of anti-VEGF in the treatment of neovascular ocular diseases. In contrast to ranibizumab and pegaptanib, randomized controlled trials evaluating the intravitreal use of bevacizumab have not yet been conducted, resulting in lack of valid and reliable safety data. In addition, most patients (especially those affected by AMD) may require long-term maintenance therapy. For this reason it is advisable to improve the current findings with further evaluations and data colletion through long lasting clinical trials, in order to better delineate the safety profile of these drugs.

ACKNOWLEDGEMENTS

None.

REFERENCES

1. Singerman LJ, Masonson H, Patel M et al for the VEGF Inhibition Study In Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group. Pegaptanib sodium for neovascular age-related macular degeneration: third year safety results of the V.I.S.I.O.N. trial. *Br J Ophthalmol* 2008; **92(12):** 1606-11

2. Brown DM, Michels M, Kaiser PK et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular agerelated macular degeneration: two-year results of the ANCHOR study. *Ophthalmology* 2009; **116(1):** 57-65

3. Rosenfeld PJ, Brown DM, Heier JS et al for the MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *NEngl J Med* 2006; **355(14):** 1419-31

4. Tolentino M. Systemic and Ocular Safety of Intravitreal Anti-VEGF Therapies for Ocular Neovascular Disease. *Surv Ophthalmol* 2011; **56(2):** 95-113

5. Day S, Acquah K, Mruthyunjaya P, Grossman DS, Lee PP, Sloan FA. Ocular Complications After Anti-Vascular Endothelial Growth Factor Therapy in Medicare Patients With Age-Related Macular Degeneration. *Am J Ophthalmol* 2011; **152(2):** 266-72

6. Engman SJ, Edwards AO, Bakri SJ. Administration of Repeat Intravitreal Anti-VEGF Drugs by Retina Specialists in an Injection-only Clinic for Patients with Exudative AMD: Patient Acceptance and Safety. *Semin Ophthalmol* 2011; **26(6):** 380-6

7. Mezad-Koursh D, Goldstein M, Heilwail G, Zayit-Soudry S, Loewenstein A, Barak A. Clinical characteristics of endophthalmitis after an injection of intravitreal antivascular endothelial growth factor. *Retina* 2010; **30(7):** 1051-7

8. Arevalo JF, Maia M, Flynn HW Jr et al. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. *Br J Ophthalmol* 2008; **92(2):** 213-6

9. Good TJ, Kimura AE, Mandava N, Kahook MY. Sustained elevation of intraocular pressure after intravitreal injections of anti-VEGF agents. *Br J Ophthalmol* 2011; 95(8): 1111-4

10. Tseng JJ, Vance SK, Della Torre KE et al. Sustained increased intraocular pressure related to intravitreal antivascular endothelial growth factor therapy for neovascular age-related macular degeneration. *J Glaucoma* 2012; **21(4):** 241-7

11. Hoang QV, Mendonca LS, Della Torre KE, Jung JJ, Tsuang AJ, Freund KB. Effect on intraocular pressure in patients receiving unilateral intravitreal anti-vascular endothelial growth factor injections. *Ophthalmology* 2012; **119(2):** 321-6.

12. Karagiannis DA, Mitropoulos P, Ladas ID. Large subretinal haemorrhage following change from intravitreal bevacizumab to ranibizumab. *Ophthalmologica* 2009; **223(4):** 279-82

13. Loukopoulos V, Meier C, Gerding H. Hemorrhagic complications after intravitreal injections of ranibizumab in patients under coumarin-type anticoagulation. *Klin Monbl Augenheilkd* 2010; **227(4):** 289-91

14. Mason JO 3rd, Frederick PA, Neimkin MG et al. Incidence of hemorrhagic complications after intravitreal bevacizumab (avastin) or ranibizumab (lucentis) injections on systemically anticoagulated patients. *Retina* 2010; **30(9):** 1386-9

15. Apte RS, Modi M, Masonson H et al. Pegaptanib 1-year systemic safety results from a safety-pharmacokinetic trial in patients with neovascular age-related macular degeneration. *Ophthalmology* 2007; **114(9):** 1702-12

16. Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal Bevacizumab Safety Survey: using the Internet to assess drug safety worldwide. *Br J Ophthalmol* 2006; **90(11):** 1344-9

17. Micieli JA, Micieli A, Smith AF. Identifying systemic safety signals following intravitreal bevacizumab: systematic review of the literature and the Canadian Adverse Drug Reaction Database. *Can J Ophthalmol* 2010; **45(3):** 231-8

18. Martin DF, Maguire MG, Ying GS et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011; **364(20):** 1897-908

TABLES

Table 1.

Table 1 - Demographic characteristics of eyes presenting adverse-effect after anti-VEGF injections	
Characteristics	Value
NUMBER OF EYES (patients)	107 (102)
Male	53
Age at the time of first anti-VEGF injection	
Mean	74.09
Range	55-93
With blood hypertension	65
With diabetes	12
With personal hystory of glaucoma	3
With AMD†	79
With DME‡	12
With CRVO§	7
With BRVO¶	4
With Macular Myopic Disease	5
Treated with bevacizumab (patients)	66 (64)
Treated with ranibizumab (patients)	35 (32)
Treated with pegaptanib (patients)	6 (6)
Eyes that received further injections with different anti-VEGFs	32 (31)
With previous cataract surgery	31
NUMBER OF INJECTIONS PER CYCLE	
Mean	3,8
Range	1-18

† Age-related Macular Degeneration
‡ Diabetic Macular Edema
§ Central Retinal Vein Occlusion
¶ Branch Retinal Vein Occlusion

Table 2.

Table 2 – Summary of complications registered in the study population

Drug received	Number of adverse events	Transient post-intervetion IOP elevation†	Sustainable IOP elevation‡	Sub-retinal Hemorrhage	Tractional Retinal Detachment	Infectious Uveitis	Systemic complications
Bevacizumab	74	60	10	1	1	1	1 episode of nausea/uneasiness and 1 episode of chest pain with acute vision loss
Pegaptanib	6	4	1	-	-	-	1 episode of blood hypertension (> 200 mmHg)
Ranibizumab	37	28	9	-	-	-	-

† Important IOP elevation registered at the first post-operatory measurement, reverted entirely after immediate instillation of anti-glaucoma drops

‡ Increases from baseline were considered significant if >5 mmHg in ≥2 consecutive follow-up visits

Table 3.

Table 3 – Ocular conditions in eyes showing complications after anti-VEGF treatment		
	Primary Ocular Disease	Eyes (Rate)
Bevacizumab group	AMD	47 (71.21%)
	DME	7 (10.61%)
	CRVO	6 (9.09%)
	BRVO	4 (6.06%)
	Macular Myopic Disease	2 (3.03%)
Ranibizumab group	AMD	33 (94.28%)
	DME	1 (2.86%)
	Macular Myopic Diseaes	1 (2.86%)
Pegaptanib group	AMD	5 (83.33%)
	DME	1 (16.67%)

Table 4.

Table 4 – Transient ocular elevation after anti-VEGF injections				
	Total injections received	Eyes (Rate)	Events occurred at the time of first intravitreal injection	Events occurred after following injections
Bevacizumab group	**<6**	53 (85.48%)	27	26
	6-12	8 (12.90%)	1	7
	>12	1 (1.61%)	-	1
Ranibizumab group	**<6**	20 (7.14%)	10	10
	6-12	7 (25%)	2	5
	>12	1 (3.57%)	-	1
Pegaptanib group	**<6**	2 (50%)	-	2
	6-12	1 (25%)	-	1
	>12	1 (25%)	-	1

Table 5.

Table 5 – IOP elevation registered in ≥2 consecutive visits. Bevacizumab group.				
Eye	Primary ocular disease	Number of injections received before the adverse event	Total injections received	Other anti-Vegf administered afterwards
1	BRVO	1	2	No
2	AMD	1	2	No
3	CRVO	-	1	Yes
4	DME	-	1	No
5	AMD	-	1	No
6	AMD	3	6	Yes
7	CRVO	1	2	No
8	Macular Myopic Disease	5	6	No
9	DME	7	9	Yes
10	AMD	1	2	No

Table 6.

Table 6 – IOP elevation registered in ≥2 consecutive visits. Ranibizumab group.				
Eye	Primary ocular disease	Number of injections received before the adverse event	Total injections received	Other anti-Vegf administered afterwards
1	AMD	5	8	No
2	AMD	2	5	No
3	AMD	-	8	No
4	AMD	4	8	No
5	AMD	-	1	Yes
6	AMD	1	3	No
7	AMD	2	3	No
8	AMD	1	3	No
9	AMD	-	1	Yes

Table 7.

Table 7 – IOP elevation registered in ≥2 consecutive visits. Pegaptanib group.				
Eye	Primary ocular disease	Number of injections received before the adverse event	Total injections received	Other anti-Vegf administered afterwards
1	AMD	1	2	NO

Table 8.

Table 8 – Other ocular complications occurred in eyes trated with bevacizumab.				
Eye	Ocular Complication	Primary ocular disease	Number of injections received before the adverse event	Total injections received
1	Sub-retinal Hemorrhage	AMD	-	1
2	Tractional Retinal Detachment	AMD	-	1
3	Infectious Uveitis	DME	2	3

Table 9.

Table 9 – Systemic complications registered in the study population					
Eye	Primary ocular disease	Systemic complication	Anti-VEGF received	Number of injections received before the adverse effect	Total injections received
1	AMD	Nausea/General uneasiness feeling	Bevacizumab	0	1
2	AMD	General uneasiness/Acute vision loss/Chest pain	Bevacizumab	0	1
3	AMD	Blood hypertension (>200 mmHg)	Pegaptanib	1	2