ORIGINAL ARTICLE

A one-year follow-up study of ocular and systemic complications of intravitreal injection of bevacizumab (Avastin)

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Abstract

Objectives: To report systemic and ocular complications within a year of intravitreal injection of bevacizumab (Avastin) in ocular neovascularisation.

Methods: The quasi-experimental (randomized without control) study was carried out at the Eye Department of Abbasi Shaheed Hospital, Karachi, from July 2008 to June 2010. It comprised 150 patients selected from the outpatient department with ocular neovascularisation through non-probability purposive sampling. After detailed history and examination, the patients were counseled for intravitreal injection Avastin (bevacizumab) which was injected into the vitreous cavity in sterile environment in the operation theatre using fully aseptic technique. The injection site was compressed for several seconds to avoid reflux when the needle was removed. Paracentesis was done following the injection as soon as possible. Patients were discharged on moxifloxcin eye drops and steroid antibiotic combination ointment at night time. They were followed up the very next day, after 2 weeks, 6 weeks, 3 months, 6 months and 1 year. Injection was repeated after 6 weeks if required and further repetition was done again after 6 weeks according to the need of the patient.

Results: Of the 150 patients, 93 (62%) were males and 57 (38%) were females. Most commonly presenting age group was between 50-60 years (n=51; 34%) followed by 41-50 years (n=41; 27.4%). Most common indication for intravitreal injection Avastin (bevacizumab) was proliferative diabetic retinopathy in 134 (89.33%) patients, followed by age-related macular degeneration (wet type) in 5 (3.3%) patients. Most frequently presenting ocular complication was subconjunctival haemorrhage seen in 35 (23%) patients, followed by regurgitation of drug from the site of injection in 8 (5.3%) patients, transient rise of intraocular pressure in 7 (4.7%) patients, mild uveitis in 4 (2.7%) patients, lens injury in 3 (2%) patients, conjunctival chemosis and iatrogenic vitreous haemorrhage in 1 (0.7%) patients. Among the systemic complications were acute rise of blood pressure in 4 (2.7%) patients, and mild irritation and allergic reaction on skin in 1 (0.7%) patient.

Conclusion: Avastin is generally a safe drug for treatment of ocular neovascularization. The complications reported were more associated with the technique of the procedure and not the drug itself and were easily manageable. Drug-related complications were limited, transient and easily managed with treatment.

Keywords: Visual aquity, Proliferative diabetic retinopathy, Retinal neovascularization, Best corrected visual acuity.
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Introduction

Bevacizumab (Avastin) a monoclonal antibody targeting vascular endothelial growth factor (VEGF), is used for systemic administration in patients with metastatic colon cancer.[1] Systemic intravenous bevacizumab therapy for colon cancer could increase the risk of cerebral infarction, transient ischaemic attacks and myocardial infarction.[2] Bevacizumab was first injected intravenously to treat age-related macular degeneration (AMD). Though no serious ocular and systemic adverse events were identified, temporary mild elevation of systolic blood pressure was reported.[3] Based on these data, the systemic administration of bevacizumab had the potential to cause systemic side effects. The use of intravitreal bevacizumab to treat ocular diseases was first reported in 2005 for choroidal neovascularisation (CNV) caused by AMD.[4] Intravitreal injection of bevacizumab is now used globally to treat diseases including CNV caused by AMD, retinal vein occlusion[5] and proliferative diabetic retinopathy (PDR).[6] Intravitreal injection of bevacizumab has also been used for iris neovascularisation with PDR,[7] CNV caused by pathological myopia[8] and idiopathic CNV.[9]

The dose used for intravitreal administration of bevacizumab for ocular diseases is about 1/400th of that administered intravenously, and the injection target is an intraocular site instead of the blood vessels. Therefore, the systemic effects caused by intravitreal injection of bevacizumab are considered to be much less than those resulting from intravenous injection. That is one reason why focal administration, instead of systemic

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administration, of this drug spread worldwide so rapidly. However, not only the potential ocular adverse events like endophthalmitis, lens damage and retinal pigment epithelial tear after intravitreal injections of bevacizumab,[6,10-13] but also the possible drug-related systemic adverse events (including hypertension and cerebral vascular accidents) have been reported recently,[11,13] though the rate is much lower than that associated with systemic administration. These reports suggested that a small amount of this drug may cause systemic effects even when the drug is administered intravitreally.

Avastin (bevacizumab) was not initially developed to treat ocular condition. Based upon the results of clinical trials that demonstrated its safety and effectiveness, Avastin was approved by the Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer.

As a condition of approval, the manufacturer produced a 'label' explaining the indications, risks and benefits. The label explains that Avastin works by blocking VEGF, which helps prevent further growth of the blood vessels that the cancer needs to continue growing. Once a device or medication is approved by the FDA, physicians may use it 'off-label' for other purposes if they are well-informed about the product, base its use on firm scientific method and sound medical evidence, and maintain records of its use and effects. Ophthalmologists are using Avastin 'off-label' to treat AMD and similar conditions since research indicates that VEGF is one of the causes for the growth of abnormal vessels that cause these conditions.

Patients and Methods

The patients were selected through non-probability consecutive sampling from the outpatient department of the Eye Department of Abbasi Shaheed Hospital, Karachi. A total of 150 patients were selected for the quasi-experimental study which was conducted from July 2008 to June 2010. Patients with diagnosed choroidal and retinal neovascularisation such as PDR, diabetic macular oedema, central retinal vein occlusion, neovascular glaucoma myopic maculopathy, and age-related maculopathy (wet type) were included in the study. Patients having ocular conditions that could effect the clarity of media as corneal opacities, uveitis, retinal detachment and glaucomas other than neovascular glaucoma were excluded.

History was taken regarding duration of the disease and decreased vision. Detailed ocular examination, including visual acuity, intraocular pressure, detailed anterior segment examination on slit-lamp and direct and indirect fundoscopy was done. Cardiac fitness was assessed to rule out any cardiac illness. Patients were counselled for intravitreal injection bevacizumab (Avastin). After detailed examination patients were admitted in the ward. After the application of topical anaesthesia, the eye and lids were disinfected with povidone iodine. Intravitreal injection Avastin 1.25mg/0.05ml was injected 3.5-4.0mm posterior to the corneal limbus into the vitreous cavity in sterile environment in the operation theatre using fully aseptic technique. The injection site was compressed for several seconds to avoid reflux when the needle was removed. Paracentesis was done following the injection as soon as possible. This also helped to prevent the regurgitation of drug from the injection site.

Patients were discharged on moxifloxcin eye drops and steroid antibiotic combination ointment at night time. Patients were followed up the very next day, after 2 weeks, 6 weeks, 3 months, 6 months, 1 year and after every 6 months till 1 year. During the follow-up period, the best-corrected visual acuity (BCVA) was measured using a Snellen's chart, and slit-lamp and fundus examinations were performed. Optical coherence tomography (OCT) and fluorescein angiography (FA) were performed if required.

Ocular and systemic complications were noted during the injection and in the follow-up period. The patients were also instructed to report any ocular changes and systemic clinical episodes after treatment.

Results

Of the 150 patients, 93 (62%) were males and 57 (38%) were females. Most commonly presenting age group was between 50-60 years (n=51; 34%) followed by 41-50 years (n=41; 27.4%) (Table-1). Most common indication for intravitreal injection Avastin was PDR in 134 (89.3%) patients followed by age related macular degeneration (wet type) in 5(3.3%) patients (Table-2).

Among the ocular complications seen at the time of injection, the most frequent was subconjunctival haemorrhage in 35 (23%), regurgitation of drug in 8 (5.3%), lens injury in 3 (2%) and Iatrogenic vitreous

Table-1: Age distribution.

Age in years	Frequency	Percentage
21-30	2	1.3%
31-40	13	8.7%
41-50	41	27.4%
51-60	51	34%
61-70	36	24%
71-80	7	4.6%
Total	150	100

Table-2: Indications for intravitreal injection avastin.

Indication	Frequency	Percentage
Proliferative diabetic retinopathy (47% patients had diabetic macular oedema as well)	134	89.3%
Central retinal vein occlusion (patients had macular oedema in addition to retinal neovascularisation)	4	2.7%
Branch retinal vein occlusion(Patients had macular oedema neovascularisation at few places)	2	1.3%
Age related macular degeneration(wet type)	5	3.3%
Myopic maculopathy	1	0.7%
Neovascular glaucoma	4	2.7%
Total	150	100

Table-3: Ocular complications.

Complications	Frequency	Percentage
Subconjunctival haemorrhage	35	23%
Conjunctival chemosis	1	0.7%
Regurgitation of drug	8	5.3%
Transient rise of intraocular pressure	7	4.7%
Anterior uveitis	4	2.7%
Lens injury	3	2%
Iatrogenic vitreous haemorrhage	1	0.7%

Table-4: Systemic complications.

Complications	Frequency	Percentage
Acute rise in blood pressure	4	2.7%
Generalized itching and irritation on skin	1	0.7%

haemorrhage in 1 (0.7%). Transient rise of intraocular pressure was seen immediately after the injection in 4 (7%) patients (Table-3).

Among the systemic complications observed immediately after the injection was acute rise of blood pressure in 4 (2.7%) patients. Generalised itching and irritation on skin was seen on the first post-injection day in 1 (0.7%) patient (Table-4).

Discussion

The dose used for intravitreal administration of bevacizumab for ocular diseases is about 1/400th of that administered intravenously, and the injection target is an intraocular site instead of the blood vessels. Therefore, the systemic effects caused by intravitreal injection of bevacizumab are considered to be much less than those resulting from intravenous injection. That is one reason why focal administration, instead of systemic administration, of this drug has spread worldwide. However, not only the potential ocular adverse events after intravitreal injections of bevacizumab[10-13] but also the possible drug-related systemic adverse events (including hypertension and cerebral vascular accidents) have been reported recently,[11] though the rate is much lower than that associated with systemic administration.

These reports suggested that a small amount of this drug may cause systemic effects even when the drug is administered intravitreally.

In our study, 150 patients with ocular neovascularisation were included. A study conducted in Japan reported that among 707 patients, 9 (1.27%) had ocular problems and eight (1.13%) had systemic problems.[14] Ocular complications possibly related to the bevacizumab intravitreal injection included corneal abrasion 2 (0.28%), chemosis 2 (0.28%), lens injury 1 (0.14%), ocular inflammation 2 (0.28%), retinal pigment epithelial (RPE) tear 1 (0.14%), and acute vision loss in 1 (0.14%) patient. The last two complications were not seen in our study.

The systemic complications included cerebral infarction 1 (0.14%), elevation of systolic blood pressure 2 (0.28%), facial skin redness 1 (0.14%), itchy diffuse rash 1 (0.14%) and menstrual irregularities 3 (0.42%). In our study, no cerebral infarction or menstrual abnormalities were reported.

In another clinical interventional case-series study, intravitreal injection bevacizumab was given in 3818 patients.[15] An infectious endophthalmitis, which necessitated pars plana vitrectomy, was detected in two eyes. Two eyes showed a painless vitreous clouding which subsided after intensified topical antibiotic therapy; one eye developed a retinal detachment, and two eyes showed a rapidly progressive cataract. None of these complications were reported in our study except the cataract formation.

Another study reported a case of herpetic keratitis 3 days after intravitreal injection bevacizumab in a 63-year-old man with PDR.[16] No such complication was reported in our study.

One study reported that out of the 19 eyes which were injected intravitreal bevacizumab from the same batch, 14 showed moderate to severe ocular inflammation

immediately after injection. Cultures of aqueous humour and vitreous from 5 eyes were negative for bacteria and fungi. Intravitreal injection of bevacizumab can cause sterile endophthalmitis. Most inflammation occurred within a few days after the intravitreous injection of the bevacizumab, but treatment with antibiotics, steroids, and/or vitrectomy was effective, and the prognosis was good in most cases.[17]

In another study, a total of 693 bevacizumab injections were administered on 193 eyes of 173 patients.[18] There were a total of 9 cases of acute intraocular inflammation for an incidence of 1.30%.

Retinal pigment epithelium detachment has also been reported as a complication of intravitreal injection bevacizumab.[14,19] This complication was also not reported in our study.

Conclusions

Avastin (bevacizumab) is generally a safe drug for treatment of ocular neovascularisation. The complications reported are more associated with the technique of the procedure and not the drug itself and are easily manageable. Drug-related complications are limited, transient and easily managed with the treatment. Careful pre-injection evaluation, per-injection and post-injection monitoring is required to minimise the risk of ocular and systemic complications.

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