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Indications for Intra Vitreal Bevacizumab (Avastin)

Dr. J. M. Lokabhi Reddy
Associate Professor, Sarojini Devi Eye Hospital, Hyderabad, India
Dr. SikandarLodhi
Assistant Professor, Sarojini Devi Eye Hospital, Hyderabad, India
Dr. Rajalingam
Associate Professor, Sarojini Devi Eye Hospital, Hyderabad, India
Dr. Srihari
Associate Professor, Sarojini Devi Eye Hospital, Hyderabad, India

Abstract:
Intra vitreal Injections are one of the modes of Ocular Drug delivery systems. Anti VEGF agent, Inj. Ranibizumab (Lucentis) was approved for treatment of Wet ARMD to stabilize the Sub Retinal New vessels. A similar Drug Inj. Bevacizumab (Avastin), approved for Colo Rectal Cancer is also being widely used for the same purpose all over the world as an off label drug. In recent times, Inj. Bevacizumab (Avastin), has become very popular and being used in Various other Ocular conditions. Bevacizumab is the predominant agent used to treat neovascular AMD worldwide [1] Since 2006, there have been reports of over fifty ocular entities being treated with Bevacizumab, generally those associated with Neovascularization or Vascular leakage as a consequence of an underlying disease [2]. This is a Retrospective study of the Data entered in Retina Dept of Government Tertiary care centre to show the changing pattern of usage of Inj. Bevacizumab (Avastin) in various conditions of the Eye between April 2014 - March 2015.
During Past one year the Indications were widening and Inj. Bevacizumab is being used and tried for some conditions which were not responding to other known treatment protocols.

Keywords: *Intra Vitreal Injections, Inj. Bevacizumab, Avastin, Ranibizumab, Lucentis*

1. Aim

To asses the trends of Various Ocular Conditions for which Inj. Bevacizumab is being given during the past one year. There is no consensus in usage of these Anti VEGF drugs (Avastin&Lucentis) among the Retina Specialists.

2. Material & Methods

This is a retrospective study from the Data available with Retina Dept. of a Govt. Tertiary Care Centre. The standard dose of 1.25 mg in 0.1ml, is administered to all cases. When repeated doses were given, the injection was given with an interval of 4-6 weeks. Three consecutive doses Avastin were given with monthly intervals in Wet ARMD cases, sometimes extending more depending on the activity or presence of fluid in Retinal layers. Routinely the injections were given under Topical Anesthesia, in Operation Theatre under full aseptic precautions. Antibiotic drops were advised 4 times per day for one week after the injection. All the cases were reviewed after 24 hrs, 1 week and 1 month later. Visual Acuity assessment, IOP, Fluoresceinangiography&/or OCT were done to assess the response.

3. Results

Common indictions for Intra vitrealAvastin injections were grouped into 4 Categories. Most common indication (41%) was being Macular edema due to various causes. The next common being the CNVM (26.4%).Inj.Avastin as Pre operative adjuvant has become one of the common indications (20.4%) , as it was facilitating the Complicated surgeries by reducing the intraOperative bleeding.

Indications for Intra VitrealAvastin	
Conditions associated with CNVM:	246 / 931 (26.4 %)
Conditions associated with Macular Edema:	381 / 931 (41%)
Pre Op TRD with Retinal New vessel formation:	190 / 931 (20.4 %)
Other Uncommon conditions:	114 / 931 (12.2 %)

Table 1

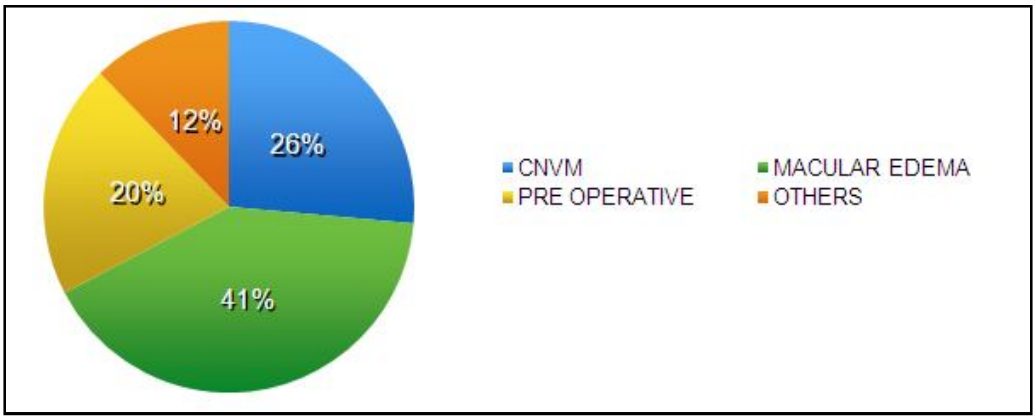

Figure 1

3.1. CNVM

Earlier most Common indication for Anti VEGF agents was CNVM of Wet Age Related Macular Degeneration. Three consecutive doses Avastin were given with monthly intervals in CNVM cases, sometimes extending more depending on the activity or presence of fluid in Retinal layers. In our study CNVM was indication in about 26% (246/931 cases). 210/246 (85%) of the cases are of Wet ARMD. CNVM in Myopia, Inflammation, Trauma, Ideopathic put together constitute 15% of CNVM cases.

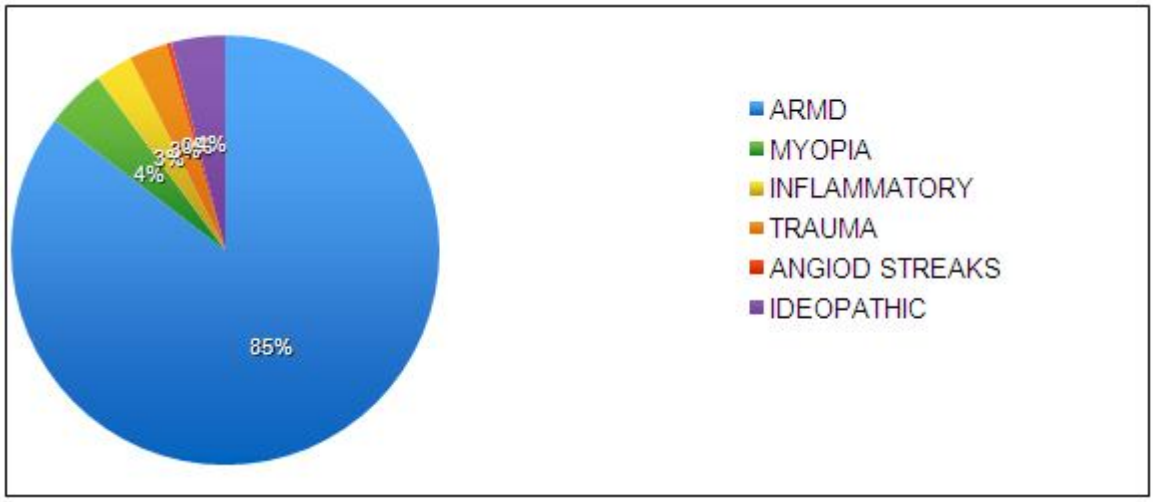

Figure 2

3.2. Macular Edema

With the positive response results in reducing the Macular edema in Vascular occlusion and Diabetic Macular edema (DME) from various studies, it has become more commonly used indication. (381/931- 41%) . DME & RVO put together constitute about 90% Macular Edema cases. Avastin was also tried occasionally where there was no response to the regular management of Post Cataract Surgery Macular edema.

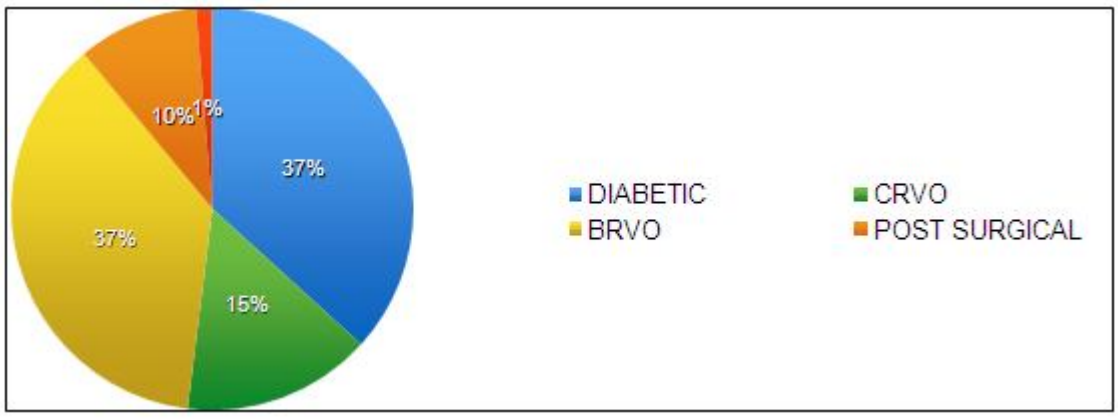

Figure 3

3.3. Pre Operative

Other condition which has become common these days is Pre operative Intra VitrealAvastin for the Vaso Proliferative conditions like PDR, Venous Occlusive disease &Eales disease to reduce intra operative bleeding. Avastin is usually given 3-7 days earlier to Surgery.

Figure 4

3.4. Uncommon Conditions

Inj. Avastin was used in some conditions to clear the media with mild Vitreous Hemorrhage and facilitate the Laser treatment. Avastin also being given in some conditions to clear Sub Retinal Hemorrhage in Macular area like Choroidal tears and IPCV. In some conditions where there is a vascular leak with deposits coming into Sub foveal area like in Coats &Lebers telangiectasia. Avastin has been successfully used to hasten the absorption of Exudates. Some Retina specialists
also tried Avastin for Chronic CSR with Sub Foveal leak.

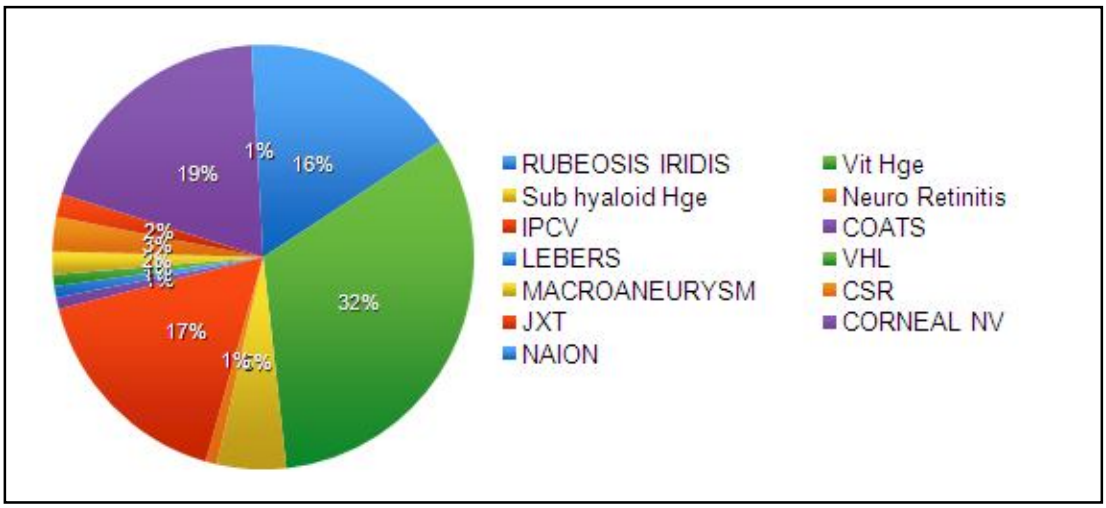

Figure 5

4. Discussion

Intra VitrealRanibizumab(Lucentis) was approved drug for Wet ARMD. Bevacizumab (Avastin) is a similar drug approved for Colo Rectal Cancer. Bevacizumab (Avastin) effectiveness is similar to that of Ranibizumab. Due to the cost effectiveness Bevacizumab has become more popular than Ranibizumab all over the world [3]. In India Inj. Ranibizumab (Lucentis/Accentrix) costs about Rs. 25,000/- per single dose. Inj. Bevacizumab (Avastin) costs around Rs. 25,000/- per 100mg in 4 ml vial , which is being used as multiple dose vial. Avastin accounts for more than 50% of anti-VEGF administrations even in US . In other developing countries it is being used more frequently. ICO (International Council of Ophthalmology) has suggested to WHO that Inj. Bevacizumab should be added to the list of Essential Eye Medicine for usage in Developing countries.

Intra VitrealAvastin injection is the off label drug used as Anti VEGF agent in Many Ocular conditions. Wet ARMD is the main indication for which the drug was being used since 2005. Later many conditions, where there was New vessel formation and Retinal Edema suspected to be due to vascular hyper permeability became the indications for Intra VitrealAvastin.

These include several types of Choroidal neovascularization, Retinal neovascularization, Macular edema, Neovascular glaucoma and Radiation-induced eye diseases.[2] Intravitreal bevacizumab administration is now used as a first line therapy for several diseases by many Retina specialists.

AMD is the leading cause of blindness in persons over 50 in developed countries.[2] It is estimated that by 2020, as many as 7.5 million people worldwide over age 65 may have vision loss attributable to AMD. [2] Ten to twenty percent of these persons are expected to have the Neovascular form of the disease 'Wet ARMD' due to the Presence of Choroidal New Vessels (CNV) with leakage), and this form of the disease is responsible for 90% of all cases of severe vision loss due to AMD [2]. If left untreated, this condition can lead to severe vision loss in low and middle income countries. Other conditions associated with CNV are Degenerative Myopia, Traumatic Choroidal Tear, Inflammatory Scar due to Choroiditis, Angiod streaks. Some CNVMs does not have any etiological factor - Ideopathic CNV. All of them respond well to Intra viral Anti VEGF agents (Bevacizumab&Ranibizumab.)

Other Common Condition Macular Edema also responds well Avastin. There are many studies which shows good response of clearing Diabetic Macular edema, Cystoid Macular edema associated with CRVO & BRVO, Uveitis also responds well to Avastin. Vascular endothelial growth factor (VEGF) has been shown to be associated with breakdown of the blood retinal barrier and increased vascular permeability thereby contributing to the development of macular edema.[4,5]

In a study of 150 Patients by Fasih et al, 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 [6]

CRUISE study suggests that monthly injections of an anti-VEGF drug may be beneficial in patients with macular edema secondary to CRVO [7].

The recently published BRAVO study randomized patients with BRVO and macular edema to monthly intravitreal injections of ranibizumab (0.3 mg, 0.5 mg) and sham. The findings of the BRAVO study may also imply that more aggressive treatment for macular edema secondary to BRVO should be considered, even in early stages (e.g., monthly injections as opposed to PRN, without watchful waiting for the macular edema to resolve), in order to avoid recurrence of the macular edema as well as to maintain optimal VA. [8]

Post Operative (after Uneventful Cataract Surgery) CME usually resolves spontaneously in about 90% of eyes and only a small subset of patients suffer permanent visual morbidity. [9]. the remaining patients mostly responds to Intra vitreal Steroids & Avastin.

Another Study of 1765 Intra virtual Avastin injections, shows Diabetic Retinopathy & Macular edema (46.45%), ARMD (26.34%), CRVO (6.6%), BRVO (9.8%) are the common conditions where Avastin was indicated in their set up in 2006-2007. [10]

In a study by Avery RL et al, all patients with neovascularization demonstrated by fluorescein angiography (44/44 eyes) had complete (or at least partial) reduction in leakage of the neovascularization within 1 week after the Avastin injection. Complete resolution of angiographic leakage of neovascularization of the disc was noted in 19 of 26 (73%) eyes, and leakage of iris neovascularization completely resolved in 9 of 11 (82%) eyes [11]. This effect helps in the Patients who are undergoing Vitrectomy to release the traction with less per operative bleeding.

Some conditions like Sub Retinal hemorrhage in macular area due to Trauma also responds well to Avastin [12]

The most common side effects in clinical trials were conjunctival haemorrhage, eye pain, vitreous floaters, increased intraocular pressure, and intraocular inflammation. Serious adverse events related to the injection procedure occurred with an incidence rate of less than 1% and included endophthalmitis, retinal detachment, and traumatic cataracts. Other serious ocular adverse events observed among ranibizumab-treated patients (incidence rate < 1%) included intraocular inflammation and blindness.

It has been shown the effect of Avastin in contralateral eye also [13,14] in some cases where there is bilateral cystoid macular edema

5. Conclusion

Intra Vitreal injection of Avastin has become one of the main treatment modalities in Many Ocular conditions. It was started for the treatment of Wet ARMD with great success. It has also shown good response in many conditions to regress the New vessels, Resolving Cystoid Macular edema & exudates. It has also proven to give better visual stability in many conditions where other modalities likeLaser& PDT could not have given improvement of vision [15,16]. Sometimes combined therapy (Anti VEGF with Laser) may help to stabilize the disease.[17] The complications are extremely rare and caution should be taken in following strict Aseptic conditions.

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