

Changing paradigms of anti-VEGF in the Indian scenario

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Anti-vascular endothelial growth factors (VEGF) agents have revolutionized the treatment of retinal diseases. Use of anti-VEGF agents in the Indian Scenario present some unique challenges considering the absence of compounding pharmacies, poor penetrance of health insurance and limited affordability of the citizens of a developing economy. To study the changing paradigms of anti-VEGF use in the Indian scenario, all articles published by Indian authors, data from web-based surveys amongst Indian vitreo-retinal specialists were reviewed. In the paucity of compounding pharmacies in India, fractionation and injection techniques differ from those of developed countries. Frequent anti-VEGF monotherapy offers the best anatomical and visual results, but economics of scale do not allow the same in the Indian scenario, resulting in PRN dosing and combination of anti-VEGF with laser photocoagulation, being the commonly employed treatment protocols.

Key words: Anti-VEGF, India, treatment protocols

Since their introduction into ophthalmology, anti-vascular endothelial growth factors (anti-VEGF) have revolutionized the treatment of many retinal diseases. Anti-VEGF agents were introduced in India around 8 years back and much has been learnt from collective experience across continents resulting in change in treatment protocols, diseases treated, case selection and complications.

Use of anti-VEGF agents in the Indian Scenario present some unique challenges resulting in indigenous improvisations, modified protocols and treatment outcomes. This article aims to summarize the use of anti-VEGF agents in the Indian scenario by reviewing literature published on anti-VEGF agents from India, part of the information gained from surveys of vitreo-retinal surgeons in India and perceived opinion of the author.

Materials and Methods

A PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) search was performed individually using the keywords pegaptanib, bevacizumab and ranibizumab. The listed articles were screened manually for publications originating from India and these were grouped based on the disease treated, agents used, date of publication and the type of publication. Attempt was made to identify any change in paradigms of treatment, such as diseases treated and modification of treatment protocols over the time frame of the articles that have been published. The articles have been grouped under disease categories as listed below:

- Age-related macular degeneration (AMD)
- Diabetic retinopathy
- Retinal venous occlusions
- Choroidal neovascular membranes (CNVM) of other etiology

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Manuscript received: 16.10.13; **Revision accepted:** 12.11.13

- Other ocular conditions
- Safety and complications and
- Miscellaneous articles

Retina practice trends study (www.retina-practice-trends.com) was a study performed amongst practicing vitreo-retinal specialists of India by a web-based questionnaire consisting of 80 questions under 7 sub-groups. One of the sub-groups was on the use of anti-VEGFs and information from the survey has also been perused.

Dr. Abishek Kothari performed Retnet Avastin Survey amongst the members of the retnet group (<http://groups.yahoo.com/group.RetNetIndia>) studying the bevacizumab usage preferences amongst Indian vitreo-retinal specialists and data from this has also been perused. Around 113–150 members of the vitreo-retinal community in India answered both the surveys.

Results

Publications by Indian based authors on anti-VEGF agents started in the year 2007, with 69 peer reviewed papers published until September 2013.^[1-69] The years between 2007-10, being populated largely by case reports and occasional case series detailing the use of anti-VEGF agents in treating CNVM of other etiology, and retinopathy of prematurity^[41] (2007), AMD^[3] and adjunct to trabeculectomy^[44] (2008). We can see a trend towards randomized case-control studies comparing different anti-VEGF agents, the use of combination treatments in AMD and other diseases since 2011 onwards.

Injection preferences and practices

In regards to the choice of anti-VEGF agent, bevacizumab is likely to be the most often used agent considering the economic burden of using ranibizumab in the developing economy of India. The lack of government aided and/or poor penetration of health insurance in the country also aid to the wide use of bevacizumab. As is the worldwide trend, pegaptanib is used seldom in India. The economic reasons also dictate the dosing pattern that is followed by most, which is loading dose of 3 monthly injections followed by

Access this article online

Website:

www.ijo.in

DOI:

10.4103/0301-4738.126189

Quick Response Code:



pro re nata (PRN) dosing for AMD and only PRN dosing for most other indications.

Use of topical antibiotics with intravitreal anti-VEGF injections

Sixty-two percent of vitreo-retinal specialists use topical antibiotic before and after intravitreal injection whereas 27.4% use it only after injection (www.retina-practice-trends.com). The trend however is to use pre- and post-injection povidone iodine (5%) in the conjunctival cul-de-sac and avoid usage of pre- and post-injection antibiotics to eliminate emergence of drug-resistant organisms.

Method of fractionating bevacizumab

Using a single vial for multiple withdrawals seems to be the most common method followed by most vitreo-retinal specialists in India. Institutional users with access to a laminar flow hood tend to fractionate bevacizumab into multiple single use syringes or ampoules, the other method being patient pooling and dispensing a single vial on a single day. An opened vial or aliquots are stored most often up to a month and less commonly up to 2 weeks (<http://groups.yahoo.com/group/RetNetIndia>). The paucity of compounding pharmacies in India and lack of access to a laminar flow hood has resulted in the practice of multiple use vials. Velpandian *et al.* documenting safety of preparing aliquots of bevacizumab in pharmacy laboratory in one study, noted the low incidence of endophthalmitis if aliquots were prepared under controlled conditions and strict protocol.^[1]

Indian vitreo-retinal specialists have reported endophthalmitis with all methods of fractionation, but in the absence of a controlled randomized study, it is improper to draw conclusions based on the survey alone (<http://groups.yahoo.com/group/RetNetIndia>).

Administration of the injection

Most tend to inject in the operating room after scrub and donning a sterile dress. A small percentage administers the injections in the side rooms of the operating theater complex and fewer still in the outpatient clinics (<http://groups.yahoo.com/group/RetNetIndia>).

We shall now look at individual disease entities.

Age-related macular degeneration

Azad *et al.* were the first to publish the results of bevacizumab for treating wet AMD in the Indian population in 2008 documenting improved vision in all AMD lesion types.^[3] In this interventional case series, mean vision improved from 20/160 to 20/100 over 6 months, decrease in central macular thickness and lesion size, and 15 letter improvement of vision in 20% of treated patients, small lesions showing better improvement than large ones.^[3]

One of the drawbacks of anti-VEGF therapy is the need for repeated injections. One of the ways to decrease the number of injections is by combining photodynamic therapy (PDT) with anti-VEGF injections. Mont Blanc and Everest studies found that the efficacy of the combination was similar to that of anti-VEGF monotherapy.^[70,71] Kumar *et al.* in India addressed this issue, which however was not a comparative study.^[5] Over 6 month follow-up, only 11.76% of the 17 treated eyes needed retreatment in this study with stabilization

of vision (gain/loss < 2 lines) in 82.24% and improvement in 17.65% of the treated eyes. These results mirror other reports indicating that number of retreatments decrease with combination of PDT and anti-VEGF, the efficacy however being similar to anti-VEGF monotherapy.^[5]

Biswas *et al.* in their study of 104 eyes found that visual and anatomical outcomes were similar with bevacizumab and ranibizumab, akin to the results of the CATT and IVAN trials.^[11,72,73]

There are no published studies from India on the impact of dosing patterns but the Retina practice trends (RPT) study revealed that most vitreo-retinal specialists would use 3 loading doses of bevacizumab or ranibizumab for AMD followed by PRN dosing based on optical coherence tomography (OCT) findings (www.retina-practice-trends.com). I perceive a move towards treat and extend protocol by most in India but the economic implications may limit the widespread use of the same.

The popularity of combined photodynamic therapy with anti-VEGF injections has also waned with the results of anti-VEGF monotherapy being similar to that of the combination therapy, while the economic burden of the combination is much higher given the added cost of the expensive photodynamic therapy.

To summarize, in regards to the use of anti-VEGF for AMD in India, most would use bevacizumab monotherapy on a loading dose followed by PRN dosing. Ranibizumab may be preferred in affordable patients and in poor-responders/those developing tachyphylaxis to bevacizumab. Combination treatments are used seldom to treat wet AMD but more often to treat polypoidal choroidal vasculopathy (PCV).

Diabetic retinopathy

Ghosh *et al.* have published one of the few comparative studies by Indian authors in the treatment of diabetic macular edema. This cross-sectional study compared macular thickness and posterior hyaloid changes after intravitreal bevacizumab in 15 patients and triamcinolone in 10 patients with no significant difference between the same.^[16] Significant changes in posterior vitreous detachment occurred in both groups but this was accompanied by decreased central macular thickness, only in the intravitreal bevacizumab group.^[16]

Studies have shown that frequent repetitive anti-VEGF injections with or without deferred laser photocoagulation achieve the best visual results in the treatment of diabetic macular edema (DME).^[74] Translating it to the Indian scenario, though anti-VEGF agents are used as the initial treatment of fovea involving diabetic macular edema, they are seldom used in isolation but almost always with subsequent laser photocoagulation. Anti-VEGF agents are primarily used on a PRN basis in the treatment of DME. Triamcinolone as an alternative is used in pseudophakic patients who are non-responders to anti-VEGF agents and for economic considerations.

Gupta *et al.* documented the use of a single injection bevacizumab prior to diabetic vitrectomy decreasing the risk of post-operative recurrent vitreous hemorrhage.^[17] This retrospective chart review showed that visual improvement at 6 months was noted in 74.5% patients treated with pre-operative

bevacizumab *vs.* 52.9% untreated patients. Recurrent vitreous hemorrhage was also noted less often in bevacizumab pre-treated patients (6.4% *vs.* 16.1%).^[17] However, the RPT survey showed that pre-operative anti-VEGF agent is not used routinely prior to vitrectomy in India by most surgeons, but for complicated vascular proliferations with high risk of intra-operative hemorrhage (www.retina-practice-trends.com).

Vein occlusions

A randomized controlled trial comparing grid laser, single/3 injections of ranibizumab + 1 session grid laser in the treatment of branch retinal vein occlusion by Azad *et al.* showed that the ranibizumab with laser groups to show better improvement than only laser group.^[20] In a study of 30 patients, with branch retinal vein occlusion of at least 6 weeks duration that were randomized to grid laser alone and single/3 monthly intravitreal injections of ranibizumab (0.5 mg/0.05 ml) followed by grid laser treatment on 7th day after the first injection, they noted >3 line improvement at 6 months most often in the ranibizumab + laser groups.^[20] The authors recommend the use of a single injection of ranibizumab followed by a single session of laser photocoagulation to treat macular edema associated with branch retinal vein occlusion.

In practice, it is perceived that anti-VEGFs form the mainstay in treating macular edema secondary to retinal vein occlusions, the injections being administered on a PRN basis. Grid and focal laser therapy after resolution of the retinal hemorrhages is often added to the treatment protocol, with some surgeons resorting to a sectorial laser photocoagulation directed at the areas of capillary non-perfusion in an attempt to decrease VEGF levels, thereby the number of injections.

Other CNVM

Case reports documenting the use of bevacizumab, ranibizumab and combination treatments such as anti-VEGF agents with photodynamic therapy have been published from India for the following indications:^[22-39]

Choroidal neovascularization associated with:

- a. Parafoveal telangiectasia type 2A (PFT)
- b. Myopia
- c. Angioid streaks
- d. Choroidal osteoma
- e. Best's vitelliform degeneration
- f. Traumatic choroidal rupture
- g. Toxoplasma scar
- h. Bietti's crystalline dystrophy.

A prospective and one retrospective case series documenting the use of anti-VEGF monotherapy or in combination with photodynamic therapy in the treatment of pathologic myopia and a retrospective case series documenting anti-VEGF to treat choroidal neovascularization associated with parafoveal telangiectasia have been published.^[22-30] In a noncomparative, consecutive, interventional case series, Mandal *et al.* showed that intravitreal bevacizumab resulted in >3 line vision improvement in 75% of patients with myopic CNVM.^[27] A retrospective comparison between PDT alone *vs.* PDT + triamcinolone *vs.* reduced fluence PDT + ranibizumab/bevacizumab to treat myopic CNVM showed visual improvement in all groups at 6 months, particularly in those treated with combination of PDT + anti-VEGF.^[24]

A retrospective chart review of 16 eyes with PFT type IIA related CNVM treated with a mean 1.9 injections ranibizumab/bevacizumab over 1 year showed significant visual improvement.^[23] Benefit of anti-VEGF to treat parafoveal telangiectasia without CNVM is however limited and temporary and is not advised.

Essentially, CNVM of other etiology are primarily being treated with PRN anti-VEGF agents with the combination of anti-VEGF and PDT having a limited role.

Other retinal disorders

One case report by Indian authors documents the use of anti-VEGF to treat aggressive posterior retinopathy of prematurity and the RPT survey indicated that 43% of the retinal specialists were not averse to using bevacizumab in infants (www.retina-practice-trends.com).^[43] However, laser photocoagulation remains the primary treatment option in managing retinopathy of prematurity (ROP), with select situations such as progression despite adequate laser photocoagulation, undilating pupil due to iris vascular engorgement being treated with half-dose of intravitreal anti-VEGF agents.

Indian authors have documented anti-VEGF use in the following conditions:^[44-57]

- a. Subconjunctival bevacizumab *vs.* mitomycin C as an adjunct to trabeculectomy (randomized controlled trial and case series)
- b. Subconjunctival bevacizumab for advanced pterygium (case report)
- c. Intracameral bevacizumab as an adjunct to trabeculectomy in neovascular glaucoma (case series)
- d. Topical and subconjunctival bevacizumab to treat corneal neovascularization (case reports)
- e. Intravitreal bevacizumab to treat Coats disease (case reports)
- f. Rubeosis iridis (case report)
- g. Anterior chamber neovascular membrane in blind eye (case report)
- h. Circumscribed choroidal hemangioma (case reports)

Conclusion

Akin to international trends, anti-VEGF agents have become the primary mode of therapy for many retinal diseases in India. Anti-VEGF monotherapy is used to treat CNVM secondary to AMD and other etiology, however on a PRN basis and combination of anti-VEGF and laser photocoagulation is used to treat macular edema in diabetic retinopathy and retinal vein occlusions.

Data on the systemic and ocular safety of the anti-VEGF agents in the Indian scenario is sparse and focused surveys aimed at these issues may help us devise treatment algorithms suited to our population.

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Cite this article as: Shanmugam PM. Changing paradigms of anti-VEGF in the Indian scenario. *Indian J Ophthalmol* 2014;62:88-93.

Source of Support: Nil. **Conflict of Interest:** None declared.