Intraocular use of bevacizumab in India: An issue resolved?

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ABSTRACT

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF), which has been approved for intravenous use in certain cancers. There is evidence of its efficacy and safety as an intravitreal drug compared with ranibizumab and aflibercept. We have, in our practice, found it to be a cost-effective treatment option for ocular diseases, which could save a large amount of public money used in various national health insurance systems. An alert issued by the Drug Controller General of India led to a virtual ban on its intraocular use in India. However, pro-active advocacy and leadership by national ophthalmological societies helped to resolve the issue quickly.

Natl Med J India 2017;30:345–7

PROLOGUE

Following a single incident of cluster endophthalmitis in an eye hospital in Gujarat, the Drug Controller General of India (DCGI) issued on 21 January 2016 a high alert notice on the use of bevacizumab. The decision not only caused consternation among Indian ophthalmologists, but also led to a virtual ban on bevacizumab for intraocular use. Multiple studies have shown the efficacy, safety and non-inferiority of the relatively inexpensive bevacizumab to ranibizumab and aflibercept. Deliberations with the concerned authorities resulted in the withdrawal of the alert notice on 11 March 2016.

MANAGEMENT OPTIONS FOR RETINAL DISORDERS

Management options for many medical retinal disorders include photodynamic therapy, laser and antivascular endothelial growth factor (anti-VEGF) agents. Among these, anti-VEGF agents are the first to have been shown to improve visual acuity, rather than just prevent loss of vision. The US Food and Drug Administration (FDA) has approved the intravitreal use of ranibizumab and aflibercept for diabetic macular oedema (DME), macular oedema in retinal venous occlusion (RVO) and wet age-related macular degeneration (AMD).

In India, a single-use vial of ranibizumab costs ₹17 500–71 000 (US$ 225–1035). A single-use vial of aflibercept costs about ₹56 700 (US$ 846) and of bevacizumab 100 mg costs about ₹28 000 (US$ 413). Ten to 18 doses of bevacizumab for ophthalmic use can be prepared from a single vial, costing ₹1500–2800 (US$ 22–41); i.e. 30–50 times less than ranibizumab and 20–38 times less than aflibercept.

As most patients who require intravitreal anti-VEGF need multiple injections, it is more expensive to use ranibizumab or aflibercept compared with bevacizumab. If the use of intraocular bevacizumab is made illegal in India, a large number of patients who need the drug will be deprived of an affordable and effective option.

Studies have shown that ranibizumab is not cost-effective compared to bevacizumab and provides no or little gain in quality-adjusted life years.[1] The FDA approved bevacizumab, a full-length monoclonal antibody against VEGF for intravenous use for metastatic colorectal cancer, non-squamous non-small cell lung cancer, metastatic renal cell carcinoma and glioblastoma. It is now known that VEGF plays a pivotal role in angiogenesis both in malignancies and choroidal neovascularization (CNV) in wet AMD, as well as in other retinal disorders including DME and RVO. In 2005, a study on the systemic use of bevacizumab for neovascular AMD[2] showed an improvement in visual acuity and central retinal thickness in both the 'study' eye and the 'fellow' eye at 12 weeks. The only adverse event was a mild increase in systolic blood pressure (SBP) that could be controlled with the use of antihypertensive drugs.

INTRAOCULAR USE OF BEVACIZUMAB: EVIDENCE FOR EFFICACY

Rosenfeld *et al*. showed that intravitreal use of bevacizumab was effective in a patient with central retinal venous occlusion[3] and in another patient with wet AMD.[4] Numerous studies on large numbers of patients (CATT trial in the USA,[5] IVAN trial[6] in the UK, GEFAL study in France,[7] MANTA in Austria,[8] LUCAS in Norway[9]) showed similar efficacy and safety of bevacizumab and ranibizumab in wet AMD.

In macular oedema secondary to RVO, the MARVEL[10] and CRAVE[11] studies have shown a similar gain in visual acuity with bevacizumab and ranibizumab at 6 months. The protocol T (Clinicaltrials.gov identifier NCT01627249) of the diabetic retinopathy research network did not find a significant difference between ranibizumab, aflibercept and bevacizumab in visual gain at 1 year in DME patients.[12] Bevacizumab has also been used in proliferative diabetic retinopathy, CNV due to various diseases and neovascular glaucoma. This has led to intensive research in the use of intravitreal bevacizumab. A PubMed search with keywords 'intravitreal bevacizumab' resulted in over 3500 publications in November 2017. Due to its usefulness and affordability, WHO has added intravitreal bevacizumab to its model list of essential medicines. Globally, bevacizumab is used more frequently than ranibizumab or aflibercept by ophthalmologists.

OFF-LABEL USE OF BEVACIZUMAB

The intraocular use of bevacizumab is off-label because the manufacturer is not interested in applying for US FDA approval. This could be because of the manufacturer's financial interest in the much more expensive option, ranibizumab (both drugs are manufactured by the same company). This may lead to more expense for patients, insurance companies or national health services of various countries. The implications are so large that in 2014 the Italian competition authority fined Roche and Novartis €182.5 million for colluding to try to impose the more expensive ranibizumab instead of bevacizumab for ocular diseases 'through an artificial distinction between the two products'.[13] The regulatory

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authority of France has officially allowed the off-label use of bevacizumab as 'temporary recommendations for use (TRU)'. The French and Italian governments have also passed laws to allow reimbursement of intravitreal bevacizumab.[13]

The attempt of regulatory authorities in the UK to prevent such cost-effective and safe use of intravitreal bevacizumab has been criticized.[13] Whether such regulations serve the best interests of patients or are influenced by the pharmaceutical industry is a matter of debate.[13]

SAFETY OF INTRAOCULAR BEVACIZUMAB

Bevacizumab contains a full molecule of IgG and is three times heavier (149 kilodalton) than ranibizumab (48 kilodalton) which is a Fab fragment.[14] Though better tissue penetration due to a smaller molecule size and higher affinity for VEGF has been suggested with ranibizumab compared to bevacizumab, the difference has not been clinically substantiated. The half-life of bevacizumab is longer than ranibizumab and the former may persist for longer in the blood after intravitreal injection. This may account for increased systemic serious adverse events (SSAE) especially gastrointestinal bleeding seen with bevacizumab in the CATT trial. However, the 2-year follow-up results of the CATT trial[5,15] show that mortality and arterio-thrombotic events were similar for bevacizumab and ranibizumab. The apparent increased systemic risk may rather be related to the difference in baseline characteristics (a higher mean age and a more frequent history of previous transient ischaemic attacks in patients in the bevacizumab group who were likely to be on antiplatelet agents), allocation bias or by chance.[15] Also, surprisingly the increased risk of SSAE with bevacizumab was seen in the needed group than the monthly regimen which may indicate an uncertain causative relationship of bevacizumab with these events. However, in the IVAN trial,[6] ranibizumab had higher arteriothrombotic events and heart failure rates compared to bevacizumab. The CATT trial showed more geographic atrophy with ranibizumab at 2 years.[5,15] A Cochrane review could not find any difference between intravitreal bevacizumab and ranibizumab for deaths and SSAE in the first 2 years of treatment.[16] Adverse events such as subconjunctival bleeding, transient rise in intraocular pressure, endophthalmitis, cataract and retinal detachment are common to all intravitreal injections including anti-VEGF agents; there is no definite evidence of any drug's superiority over the other in terms of these adverse events. In the CATT and IVAN trials there was no difference between endophthalmitis rates with bevacizumab compared to ranibizumab.[15] In a large study, there was no report of endophthalmitis in 1184 bevacizumab injections and in only 1 of 471 ranibizumab injections.[17] The rate of endophthalmitis following intravitreal anti-VEGF agent use has been reported to be 0%–0.092%,[18] which is much lower than the reported incidence of acute onset endophthalmitis following cataract surgery (0.04%–0.2%).[19]

Most cluster endophthalmitis occur because of either suboptimally compounded bevacizumab aliquots or fake bevacizumab. The other causes of post-intravitreal injection endophthalmitis include sterilization failure and deviation from strict asepsis during the procedure.[20]

ACTION BY INDIAN OPHTHALMOLOGICAL SOCIETIES

Following the alert notice by the DCGI, the All India Ophthalmology Society–Vitreo Retina Society of India and the DCGI constituted an expert committee. The DCGI, on the recommendations of the expert committee, withdrew the high alert on 11 March 2016. It was also agreed that a Kezzler code would be introduced by the manufacturer to prevent the use of spurious or counterfeit bevacizumab. The Kezzler code is a unique alpha-numeric code printed on each vial of the drug. The validity and genuineness of the drug can be confirmed from the manufacturer directly by messaging the code using the short message service (SMS). The manufacturer agreed to be responsible for the sterility and purity of bevacizumab and to ensure a proper documented cold chain before delivering it to the authorized distributors. Standard guidelines and a standard consent form for intravitreal bevacizumab as per international criteria were also formulated. According to this guideline,[21] the drug must be procured from only an authorized dealer and the cold chain log record should be checked periodically. To prevent wetting of the bevacizumab carton, it should be stored at 2–8 °C in a clean, air-tight plastic container. After buying the drug, it should be transported in a dry ice pack and stored in an exclusive refrigerator with temperature log, temperature display and power backup. A separate register for bevacizumab use should be maintained and should contain the names of persons who kept the vial, lot number, date of preparation and results of sample culture. The distributor and authorities should be informed of the lot number if the culture is positive.

Bevacizumab is available only in 100 or 400 mg vials. However, its intraocular dose is merely 1.25 mg and thus there is a need to prepare separate smaller aliquots for each patient. The ideal scenario would be the availability of vials with a smaller quantity of drug provided by the manufacturer. In its absence, the three possible options for preparation of injectable bevacizumab were detailed in the guidelines.[21] The aliquots/ampoules of the drug can be prepared in a 'class 1000 environment under a class 10 laminar hood and thermosealed'.[21] The second option is fractionation of the drug in 1 ml syringes under ISO class 5 conditions. The last and least preferred option is to withdraw the drug directly from the vial for multiple patients. It is imperative for all ophthalmologists to use bevacizumab judiciously, ensuring all outlined aseptic precautions and also for the manufacturer to ensure supply of the genuine drug for the benefit of patients with diseases that are amenable to treatment with its intravitreal use.

CONCLUSION

The present literature does not provide evidence of superiority of ranibizumab or aflibercept over bevacizumab in terms of safety and efficacy, whereas bevacizumab is definitely cheaper and more affordable. In India, the high alert put ophthalmologists in a legal and ethical dilemma. Commercial entities must not be allowed to dictate which drug should be used for which disorder. The safety of the patient must be the paramount concern and physicians and governmental agencies must ensure this by fair drug compounding practices. A strong leadership of national and international ophthalmological societies is needed to represent the scientific facts regarding bevacizumab to drug regulatory agencies globally. Legislation is required to prevent the circulation of fake drugs. Vision loss due to ocular infections following bevacizumab injection is usually attributed to suboptimal compounding procedures, non-compliance with standard guidelines, poor aseptic technique[22] or the use of a fake drug.

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