Review Article

Emergence of Bevacizumab as Biosimilar with Ophthalmologic Prospects for Patients and Pharma Industry

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ABSTRACT

Vascular Endothelial Growth Factor (VEGF) inhibitors, ranibizumab, aflibercept, and pegaptanib are the approved treatments for certain eye diseases that are used especially in the elderly patients. However, these drugs are mostly inaccessible due to their high cost. Bevacizumab a VEGF inhibitor approved for cancer treatment, being a cheaper alternative, is reported to be used extensively as off-label Intravitreal injection for the treatment of eye diseases. In this article, we have analyzed similarities and differences between bevacizumab and ranibizumab, and their potential application for eye disorders with long-term safety concerns. We have also analyzed regulatory and ethical aspects of off-label use to provided recommendations on this issue. Based on the extensive clinical data, actions taken, and recommendations provided by agencies such as the National Institute for Health and Care Excellence, International Council of Ophthalmology, United Kingdom and Thailand regulatory agency. There seems to be adequate evidence for controlled licensing of the claims of better safety for ranibizumab as compared to bevacizumab. However, at the expense of non-affordability, it cannot be considered positive risk-benefit scenario. Intravitreal bevacizumab is being used and will continue to be used in the list of off labels, if it is allowed by the regulators. Licensing will ensure the availability of intravitreal bevacizumab to the patients with eye diseases, without any legal or ethical concerns for the clinicians, and will also assist in generating long-term safety data. Safe delivery formulation and dosage form should be considered for approval. It is concluded that both the regulatory agencies and technical experts should join to take a critical decision and that will be a big step forward in making a cost-effective drug available to the public.

INTRODUCTION

Monoclonal antibody therapy is a type of immunotherapy that utilizes Monoclonal Antibodies (mAb) to bind mono-specifically to definite cells or proteins and thereby stimulates the patient's immune system to kill the cancerous cells. In 1986, Orthoclase OKT3® (muromonab-CD3) became the first monoclonal antibody approved by the FDA. In radio-immunotherapy a dose that is radioactive, localizes a target cell line, releasing lethal chemical doses [1]. Recently, antibodies are being used to bind to molecules that are involved in T-cell regulation to eliminate inhibitory pathways. They chunk T-cell responses and this process is known as immune checkpoint therapy [2]. It is

likely to create a mAb which is specific to almost any extracellular/cell surface target. Research and development department is underway to generate antibodies for diseases such as rheumatoid arthritis, multiple sclerosis, Alzheimer's disease, Vaccine for Ebola virus and various types of cancers [3].

There are four major types of antibodies that have been developed. They are murine, chimeric, humanized and human and each type of antibody is distinguished by the suffixes on their name:

Murine (suffix- *omab*): These were the first therapeutic antibodies murine analogues characterized by a short half-life *in-vivo* (due to immune complex formation). They have restricted penetration into tumor sites and inefficiently recruit host effector functions more immunogenic in nature [4].

Chimeric (suffix- *ximab*) and Humanized (suffix- *zumab*): These have been developed with the purpose of reducing murine antibody immunogenicity. To achieve this were engineered to be removed immunogenic substance and chimeric and humanized antibodies are produced. Thus, chimeric antibodies are made up of murine variable regions merged onto human constant regions. Human gene sequences from the kappa light chain are taken IgG1 heavy chain are mixed to produce antibodies such that humanized portion is approximately 65%. This not only reduces immunogenicity but also increases serum half-life.

Human monoclonal antibodies (suffix- *umab*): These antibodies are produced with the help of transgenic mice or phage display libraries by transferring human immunoglobulin genes specifically into the murine genome and vaccinating the transgenic mouse in opposition to the desired antigen. This leads to the production of suitable monoclonal antibodies [5]. Murine antibodies *in-vitro* transformed in this manner are then fully developed human antibodies [6]. The heavy and light chains of human IgG proteins are articulated in structural polymorphic (allotype) forms. Human IgG allotype is one of the many factors that can put in to immunogenicity [7,8].

VASCULAR ENDOTHELIAL GROWTH FACTOR

Vascular Endothelial Growth Factor (VEGF) is a large lipoprotein molecule occurring naturally in the body and made up of at least 6 structurally related proteins. Its role is displayed in various pathophysiologic processes including disease like Acute Macular Degeneration (AMD) and diabetic retinopathy. Studies have shown high VEGF levels in areas where laser-induced choroidal neovascularization in primates, and clinically in AMD patients. VEGF is a potent mitogen particularly for endothelial cells, that increases vascular permeability, and promotes leukocyte induced damage in retinal endothelial cells. Unhealthy tissues intake and release at angiogenic growth factors that are known to bind to specific receptors are located on the endothelial cells of preexisting blood vessels. After activation of endothelial cell, the cell begins to produce novel molecules and enzymes, that enzymes act on the basement membrane covering all the existing blood vessels and lead to the formation of holes in the membrane. The endothelial cells proliferate and travel out through these holes towards the unhealthy tissue. The adhesion molecules such as integrins, promotes formation of new blood vessel and Matrix Metalloproteinase (MMP) liquefy the tissue near the sprouting vessel tip to accommodate it. Finally, smooth muscle cells (pericytes) give structural support to these newly formed blood vessel loops and then blood flow begins in these vessels. The VEGF acts as a rate-limiting step in the process of angiogenesis. It also enhances vascular permeability by leukocyte-mediated endothelial cell injury, development of fenestrae, and dissolution of tight junctions. This results into intraretinal fluid accumulation and contain a negative effect on visual acuity. furthermore, VEGF can also create release of inflammatory cytokines which further reinforces the process of inflammation and angiogenesis. Thus, anti-VEGF agents may have therapeutic potential for the treatment of AMD patients [9].

Bevacizumab, introduced as recombinant humanized monoclonal antibody in 2004, is the first angiogenesis inhibitor used clinically for the treatment of cancer [10]. It was developed on the bases of the discovery of human Vascular Endothelial Growth Factor (VEGF), which is a protein responsible for stimulation of blood vessel growth, took place in the laboratory of Genentech scientist Napoleone Ferrara [11-13]. Ferrara later confirmed that antibodies against VEGF hinder tumor growth in mice [11]. His work also validated the hypothesis of Judah Folkman, proposed in 1971, stopping the angiogenesis can be useful in controlling tumor growth [12].

Bevacizumab was originally obtained from a mouse monoclonal antibody generated from mice immunized with the 165-residue form of recombinant human vascular endothelial growth factor. It was humanized by keeping the binding region and replacing the left over with a human full light chain and a human shortened IgG1 heavy chain, with some other substitutions. The plasmid thus obtained is transfected into Chinese hamster ovary cells which are grown in industrial fermentation systems[11].

Table 1: Summary of Product Characteristics and Avastin Summary of Product Characteristics [14].

Characteristics	Bevacizumab	Ranibizumab
Structure	Recombinant full monoclonal antibody which is humanized	Recombinant fragment (Fab) monoclonal antibody which is humanized - IgG1 kappa isotype
Source	Chinese Hamster Ovary cells	*Escherichia coli* expression system
Molecular weight	149 kD	48 kD
Formulation	Trehalas dihydrate; sodium phosphate; polysorbate 20; water for injection	α,α-trehalas dehydrate; histidine hydrochloride, monohydrate; histidine; polysorbate 20; water for injection
Route of administration	Intravenous	Intravitreal
Formulation and strength	25 mg per mL 100 mg in 4 mL and 400 mg in 16 mL in vial	100 mg in 4 mL and 400 mg in 16 mL in vial 10 mg per mL and 6 mg per mL 0.3 mg in 0.05 mL and 0.5 mg in 0.05 mL in vial and prefilled syringe
Dosage	5-15 mg per kg	0.3 mg or 0.5 mg
Development plan	Developed only for systemic administration in cancer	Developed only for AMD
Nonclinical studies	No studies have been reported for eye toxicity after intravitreally administration	Toxicity studies in intravitreally administration have been demonstrated
Developmental clinical studies	Systemic studies for effects in eye intravitreally not done.	Demonstrated for effects in the eye intravitreally
Therapeutic indications	Different cancer diseases	Different eye diseases

Bevacizumab is a monoclonal antibody approved for use as intravenous infusion types of cancers. However, ranibizumab is a monoclonal antibody with an antigen-binding fragment (Fab) antibody, a humanized - IgG1 kappa isotype that was approved as intravitreal injection for certain eye diseases. Both bevacizumab and ranibizumab bind to VEGF and prevent the interaction between VEGF and respective receptors, thereby, reducing the proliferation of endothelial cells and formation of new blood vessels. The differences between bevacizumab and ranibizumab are presented in Table 1 [14].

Bevacizumab is defined as a full-length, humanized monoclonal antibody which is directed against all the isoforms which are active biologically, of VEGF-A [15]. It is also known as recombinant IgG1 antibody having molecular weight of about 149kD, produced in a Chinese Hamster Ovary mammalian cell expression system with a nutrient medium having the antibiotic gentamicin. AVASTIN® (bevacizumab) looks a clear to slightly opalescent, neutral to pale brown, sterile solution having pH 6.2. It was initially designed for Intravenous (IV) infusion and is used to supplied in 100 mg and 400 mg, preservative less, single-use vials to provide 4 mL or 16 mL of AVASTIN ® (25 mg/mL). The product is formulated in various solutions depending on the requirement like alpha-trehalose dihydrate, sodium phosphate (monobasic, monohydrate), sodium phosphate (dibasic, anhydrous), polysorbate and water for injection [16]. Bevacizumab attaches to the receptor-binding area of all VEGF-A isoforms. therefore, it prevents the dealings between VEGF-A and its receptors (Flt-1 and KDR) on the surface of endothelial cells, responsible to start the intracellular signaling pathway which leads to endothelial cell proliferation and formation of new blood vessels [15].

BEVACIZUMAB AND OTHER MONOCLONAL ANTIBODIES

Bevacizumab and perception of the ophthalmologists

Through market research, various reports and open-end interviews of ophthalmologists, we found that doctors are very much satisfied with the effect and use of bevacizumab in the treatment of wet AMD. However, they are not comfortable sharing it openly because of off-label use related legal issues. Perception of ophthalmologists is quite positive when it comes to using or recommending bevacizumab in ophthalmology. In a multicenter, randomized clinical trial authors from Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group have reported the effects of ranibizumab and bevacizumab when administered monthly or as needed for 2 years and described the impact of switching to as-needed

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treatment after 1 year of monthly treatment. They reported that ranibizumab and bevacizumab had similar effects on visual acuity over a 2-year period. However, they have concluded that there were no differences between drugs in rates of death or arteriothrombotic events. The interpretation of the persistence of higher rates of serious adverse events with bevacizumab was uncertain because of the lack of specificity to conditions associated with inhibition of VEGF [17].

Multiple uses of bevacizumab in the ophthalmology

Effectiveness of ranibizumab to treat Diabetic Macular Edema (DME) has been proven with huge clinical trials. Whereas, for bevacizumab merely two clinical trials have been available and a head-to-head comparison is lacking to date [18]. However, if proved non-inferior to ranibizumab, use of the off-label bevacizumab may reduce costs extremely without a loss in visual insight. A cost-effectiveness analysis has been designed to authenticate this hypothesis. In many large randomized clinical trials, those patients who were treated with ranibizumab had a better visual result than those treated with sham injections and/or laser therapy. Ranibizumab when given as monthly injections, or in an 'as needed' scheme, resulted to a 6-10 letters better mean visual acuity after 12 months as compared to control groups [19]. The maximum effect of ranibizumab was recorded around 6 months, after which the outcome stabilized. Adding up to its effect on visual acuity, ranibizumab noticeably decreased retinal thickness when measured by Optical Coherence Tomography (OCT) and significantly enhanced patient reported quality of life parameters [20].

Bevacizumab (Avastin) is the full-length anti-VEGF-A antibody and from which ranibizumab is derived. It has been used off-label on a widespread scale by eye specialists in the US and Europe, and has increasingly become standard care in the treatment of DME in the Netherlands. Hence, we should also consider it since, results of the ranibizumab RCT's became available in 2009. The efficacy and safety measures of bevacizumab 1.25 mg in the treatment of DME have been verified in several case series and two RCTs. Bevacizumab was found responsible in the improved visual acuity by approximately 8 letters at 3-12 months follow up. Bevacizumab markedly reduced retinal thickness on OCT, to a similar amount as reported for ranibizumab [20,21]. In a multicenter clinical trial, bevacizumab at a dose of 1.25 mg were given to 218 participants, authors have reported that bevacizumab was effective and relatively safe treatments for diabetic macular edema causing vision impairment. However, at worse levels of initial visual acuity, aflibercept was more effective than bevacizumab at improving vision [22].

Pharmacogenomics and bevacizumab

In the field of ophthalmology, pharmacogenetic concept is there in existence for more than a century. Genetic variation not only helps to the susceptibility of an individual to disease but also response to therapy as well as adverse effects. Therefore, pharmacogenomics studies may offer an opportunity to minimize ADRs to therapies and increase the efficiency of medicine in a manner which is cost effective too by developing a personalized medicine. Furthermore, these studies have already shown the association of various genotypes or haplotypes with responses to drug therapies in other fields. Additionally, because of the reason that human retinal dystrophies are clinically and genetically different disorders, genetic testing will participate in an ever-increasing crucial role [23]. In the future, there are high chances that it will become a standard practice to complement the ophthalmic evaluation [24].

Regulatory approval

Bevacizumab acknowledged its very first approval in the United States in the year 2004, for combination use along with standard chemotherapy treatment for metastatic colon cancer [25]. In 2008, it was approved to treat breast cancer by the organization FDA, but that approval got revoked on 18 November 2011 [26-28]. This revoke process of approval happened because, even though there was confirmation that it slowed succession of metastatic breast cancer. However, there was lack of evidence that it extended life or better quality of life, also it caused adverse effects which includes severe hypertension and hemorrhaging. While in 2008, the FDA gave bevacizumab provisional approval to treat metastatic breast cancer, subject to further studies.

The FDA's advisory board had recommended against approval [29]. Later, in July 2010, after new studies failed to explain a significant benefit, the panel of FDA's advisory recommended against the indication for advanced breast cancer. That time, Genentech requested a hearing, granted in June 2011. The

FDA ruled to remove the breast cancer indication dated in November 2011. FDA approval was mandatory for Genentech to market a drug for that indication. Doctors may at times prescribe it for that indication, although insurance companies are less in favor to pay for it [29]. The drug was still approved for the treatment of breast cancer in other countries including Australia [30]. It has been funded by the English NHS Cancer Drugs Fund but in January 2015 it was proposed to remove it from the approved list [31].

Cost and price control

In India, comparison of bevacizumab vs. ranibizumab, showed that ranibizumab costs INR ₹70160/0.5 mg (1 vial) whereas bevacizumab costs INR ₹32250/100 mg (1 vial). From the comparison of maximum retail price of both the molecules, we can estimate the cost effectiveness of bevacizumab molecule. Hence, if bevacizumab as an ophthalmic entity enters in the market of the wet AMD can give tough competition to the rivals.

It is a well-known that bevacizumab is cost-effective as compared with ranibizumab. In India, a single use vial of ranibizumab expenses around INR ₹17,500 - ₹71,000; a single use vial of aflibercept is of around INR ₹56,700; and bevacizumab 100 mg/4 mL vial overheads around INR ₹28,000. As the required ophthalmic use dose of bevacizumab is 1.25 mg, up to 10 - 18 doses of bevacizumab molecule can be prepared from a single 100 mg vial, costing INR ₹1000 - ₹2000 per dose, that is 30 - 50 times cheaper than ranibizumab. These calculations assume the stable cost of ranibizumab [14].

The countries with national health care systems (such as in UK and Canada), many of those national health services have constrained bevacizumab on the basis of cost-benefit calculations. In the UK, for instance, the National Institute for Health and Care Excellence had proposed that bevacizumab should not be funded by the NHS since, it costs nearly GBP £21,000/ patient serving only minimal benefit in many cancers [32]. In 2006, the Scottish Medicines Consortium recommended against the NHS funding Avastin for first-line treatment of metastatic carcinoma of the colon or rectum, because of estimated costs of GBP £24,000 to £93,000 per quality-adjusted life year (QALY) [33].

The adding up of bevacizumab to standard treatment can prolong the lives of lung cancer patients by several months, which costs for USD $100,000 a year in the United States [34]. For colorectal cancer, Robert J. Mayer reported in the New England Journal of Medicine that bevacizumab has the extended life by 4.7 months (20.3 months vs. 15.6 months) in the initial study, at a cost of USD $42,800 to $55,000. Costs in other countries vary; in Canada it is reported to cost USD $40,000 CAD per year [35]. In September 2018, Bayer and Novartis Pharmaceuticals UK claimed and argued that 12 clinical commissioning groups were performing illegally using bevacizumab to treat patient with wet age-related macular degeneration were rejected by the High Court of Justice [36,37].

Specialty drug

On September 16, 2014, Genentech reclassified this molecule as a specialty drug. Specialty drug is those which are only available through specialty pharmacies. "Specialty drugs usually come under the FDA's Risk Evaluation and Mitigation Strategy (REMS) program, which is established for compounds like the testosterone that may show some unusual side effects; or for drugs that are unusually expensive". This has caused apprehension to hospitals as the price increased. According to a report of IMS Health, the average price charged by hospitals for bevacizumab is around USD $9000 compared to approximately USD $2300 this is when administered in a doctor's personal clinic. As a result of the novel distribution arrangement, many hospitals will no longer be eligible for the 51% discount to average wholesale price that was mandated by the Affordable Healthcare Act under the old distribution arrangement [38].

PHARMACOLOGICAL APPLICATIONS OF BEVACIZUMAB

Bevacizumab was approved in the United States in February 2004, for use in metastatic colorectal cancer when used with standard chemotherapy treatment (as first-line treatment) and with 5-fluorouracil-based therapy for second-line metastatic colorectal cancer. European Medicines Agency (EMA) in January 2005, approved it for the treatment of colorectal cancer [39]. Bevacizumab has also been tested as an add on therapy to other chemotherapy medicines in people having non-metastatic colon cancer. The statistics from two large randomized studies showed no benefit in preventing the cancer

from reoccurring and a potential to create harm in this setting [40].

Lung cancer

Bevacizumab was approved by the U.S. Food and Drug Administration (FDA) In 2006 for use in first-line advanced non-squamous non-small cell lung cancer in combination with carboplatin/paclitaxel chemotherapy. The basis of approval was on the pivotal study E4599 conducted by the Eastern Cooperative Oncology Group, which confirmed a two-month improvement in overall endurance in patients treated with bevacizumab. A preplanned study of histology in E4599 demonstrated a four-month median survival profit with bevacizumab for people with adenocarcinoma that represents approximately 85% of all non-squamous cell carcinomas of the lung.

In 2009, a consequent European clinical trial, AVAiL, was first reported and confirmed the significant development in progression-free survival revealed in E459. A general survival assistance was not seen in patients treated with bevacizumab; however, the reason of this may be because of the more limited use of bevacizumab as maintenance treatment in AVAiL versus E4599. Being an anti-angiogenic agent, no mechanistic underlying principle is there for restricting bevacizumab before disease progression. Stated another way, the survival benefits achieved with bevacizumab can only be projected when it is used in accordance with the clinical evidence: sustained until disease progression or treatment-limiting side effects.

Another large European-based clinical trial having bevacizumab in the treatment of lung cancer, AVAPERL, was reported in October 2011. First-line patients were treated by bevacizumab in combination with cisplatin/pemetrexed for four cycles, and after that randomized to receive maintenance treatment with either bevacizumab/pemetrexed or bevacizumab alone until the disease progresses. This maintenance treatment with bevacizumab/pemetrexed showed a 50% reduction in risk of progression vs. bevacizumab alone (median PFS: 10.2 vs. 6.6 months). Maintenance treatment with bevacizumab/pemetrexed did not confer a significant increase in overall survival vs. bevacizumab alone on follow up analysis [40].

Breast cancer

The FDA, in December 2010 notified its intent about removing the breast cancer indication (approved in 2008) from bevacizumab, saying that it had not shown to be safe and effective in the treatment of patients having breast cancer. The collective data from study of four different clinical trials showed that bevacizumab neither extended overall survival nor slowed disease progression sufficiently to outweigh the risk it presents to patients. This was the only reason which prevented the pharmaceutical company Genentech from marketing bevacizumab for breast cancer. However, doctors feel free to prescribe bevacizumab off label, although insurance companies are less likely to approve off-label treatments [26,41].

Brain cancer

Bevacizumab slows tumor growth but does not affect overall survival in people with glioblastoma multiforme [42]. The FDA established accelerated approval for the treatment of recurrent glioblastoma multiforme in May 2009 [43]. A 2018 Cochrane review can not be a good evidence for its use in recurrences either [42].

Renal cancers

In certain renal (kidney) cancers, bevacizumab improve the progression free survival time but not survival time. In 2009, the FDA approved this molecule for the treatment of metastatic renal cell cancer (a form of kidney cancer) [44-47].

Therefore, the advantages of bevacizumab over other drugs in the treatment of cancer can be compared with following:

- Cost effectiveness
- Well established market share
- Strong competitor of ranibizumab
- Doctors' Perception
- Mode of action (One of the first FDA approved anti-VEGF mAb)

Ophthalmology

Department of retinal disease management has witnessed remarkable advances in posterior section pharmacotherapy with the development of anti-VEGF molecules like Lucentis® (ranibizumab), Eylea® (aflibercept), and off-label bevacizumab (Avastin). The US patents for ranibizumab and aflibercept will expire in 2020. However, Regeneron has indicated that it may challenge to extend its US patent to June 2023 by filing additional patent claims, and their European patents will be facing expiry in 2022 and 2025. Aflibercept

becomes off patent in 2022 in People's Republic of China and Japan [48]. Once each patent expires, biosimilar molecules can strongly come in the mainstream clinical practice as a more cost-efficient option in the form of generic biosimilar. It is hard to predict that how significant this shift would be in terms of more cost-effective clinical management and how it is going to impact the healthcare world in developed and developing economies. Hence, it becomes important for clinicians to have a clear understanding about ophthalmic biosimilar.

OFF- LABEL USE OF BEVACIZUMAB

Off label use is a balance between ethics and legal/regulatory status. Drugs are produced to improve the quality of life of humankind. Pharmaceutical companies succeed on the profit generated by drugs, however if the fundamental necessities of patients are not fulfilled, the entire drug development cannot be justified. Prescription of an off label drug should be considered ethical when the drug is cost-effective, patient cannot afford another approved drug, and if enough safety data exist [49].

Though not formally studied or approved for any intraocular disease, Rosenfeld's pioneering work and the unavailability of a related ocular drug, ranibizumab, led to rapid and wide use of bevacizumab all over the world [50,51]. After initial studies were done with IV injections, this route of administration was not generally accepted due to higher costs and due to a more conceivable risk of systemic side-effects [51,52].

Off-label use is generally legal unless it violates ethical guidelines or safety regulations. The ability to prescribe drugs for uses beyond the officially approved indications is commonly used to good effect by healthcare providers. For example: methotrexate is commonly used off-label because its immunomodulatory effects relieve various disorders. Hydroxychloroquine is an anti-malarial drug despite of this fact, it is widely being used in the treatment of COVID-19 all over the world because it has shown positive effects on the patients of COVID-19. However, it is not approved by FDA for this indication [53]. Similarly, Avastin (Bevacizumab) being used in the treatment of wet-ARMD. However, off-label use can entail health risks and differences in legal liability. Marketing of pharmaceuticals for off-label use is usually prohibited. Furthermore, in a recent report, Outlook Therapeutics Inc. seeks the first FDA-approved ophthalmic formulation of bevacizumab "Bevacizumab-vikg (ONS-5010/Lytenava,)" for use in retinal indications. It is the investigational ophthalmic formulation of bevacizumab under development to be administered as an intravitreal injection for the treatment of wet AMD and other approved retinal diseases [54].

MARKET SCENARIO OF BEVACIZUMAB

Global bevacizumab is driven by factors such as rising incidences of tumor and cancer. Additionally, sedentary lifestyle leading to acute illness also propels the global bevacizumab market. Moreover, rising geriatric population is anticipated to fuel the market growth in the forecast period. However, higher medication cost is likely to impede the market growth in the forecast period. Global Bevacizumab Industry geographically spans North America, Latin America, Europe, Asia-Pacific, Middle-East and Africa. North America and European market are expected to grow at a higher CAGR in the forecast period owing to rise in prevalence of cancer and tumor patients. Moreover, increasing R&D in cancer is also expected to boost the market growth.

Asia-Pacific regions such as China, Japan and Singapore are anticipated to boost the market growth owing to large consumer base and growing prevalence of cancer patients. Middle-East and African market is expected to grow at a moderate CAGR in the forecast period owing to rising medical infrastructure and growing R&D activities in the global bevacizumab industry. The key players in the global bevacizumab industry include Pfizer, Biocon, Bionomics, Genexine, Amgen, Levolta Pharmaceuticals, Enzon Pharmaceuticals, Marsala Biotech, Mabtech, and Fujifilm Kyowa Kirin Biologics (Table 2).

In 2014, the NSCLC market (total of US$5.4 billion) was dominated by sales of three branded agents the chemotherapy drug pemetrexed (Alimta; Eli Lilly) of which erlotinib and bevacizumab held a combined 70% market share. Despite the patent expiry and ensuing competition from generic and biosimilar agents during our 2014–2024 forecast period, the NSCLC market is projected to increase to approximately $14.3 billion in 2024 with a 10% annual growth. Sales growth might be fueled by the entry of premium-priced agents, including the six therapies approved by the FDA in 2015 [55].

Table 2: Details of all the three drugs serving to wet AMD.

Molecule	Company	Brand Name	Indian/ MNC	Launch Date	MRP (INR)	Approved Pharmacological use	Off Lable Uses	Approving Regulatory Bodies
Bevacizumab	Roche & Co.	Avastin	MNC	Jul-2005	32250/100mg (1 vial)	Breast cancer, colon cancer, renal cancer, ovarian cancer etc.	Yes	USFDA, EMA
Ranibizumab	Novartis	Lucentis	MNC	Aug-2012	70160/0.5 mg (1 vial)	Wet age-related macular degeneration	No	USFDA
Aflibercept	Bayer Zydus	Eylea	MNC	Nov-2011	48000/40 mg (1 vial)	Wet age-related macular degeneration	No	USFDA

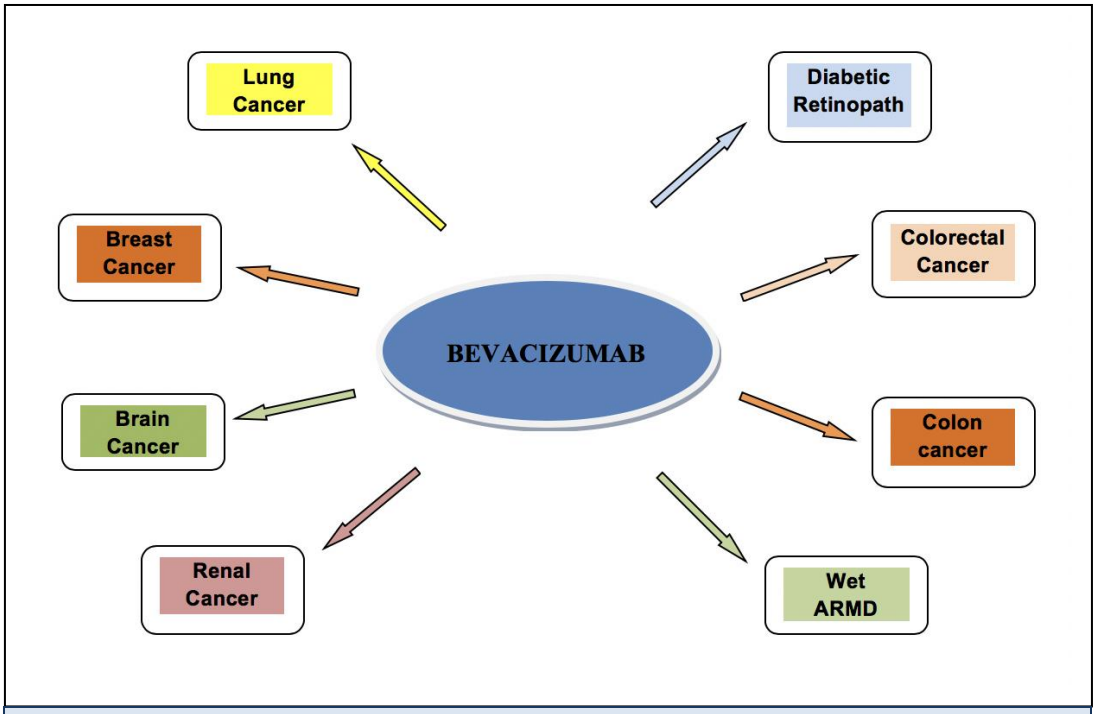

Figure 1: Pharmacotherapeutics of Bevacizumab.

CONCLUDING REMARKS

Though data from controlled trials are lacking, bevacizumab appears to be safe and effective in the short term. The evidence for efficacy and safety is increasing, but the quality of the studies is still low compared to controlled multicenter trials for drug approval. The physician must be aware of their responsibility towards the patient. This not only includes the risks associated with the off-label use, but also the cost problem and the availability of approved drugs for different ocular pathologies.

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