The Controversies Surrounding Bevacizumab and Ranibizumab

Ee Vien Low* and Faridah Aryani Md. Yusof

*Pharmaceutical Services Division, Ministry of Health, Malaysia.

Authors’ contributions

This work was carried out in collaboration between both authors. Author EVL wrote the first draft of the manuscript. Author FAMY prepared the conceptual framework of the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Age-related macular degeneration (AMD) is a leading cause of visual impairment and blindness. Both bevacizumab and ranibizumab are anti-vascular endothelial growth factors used for treatment of AMD. However, the use of bevacizumab remains controversial as it was not approved for intravitreal use although there were several head-to-head comparison trial that shows that it was non inferior to ranibizumab. Despite the status of off-label, intravitreal bevacizumab is being used worldwide as it is 30-50 times cheaper than intravitreal ranibizumab. The case of intravitreal bevacizumab illustrates the use of “not-me” drug and different countries responds differently to its use.

Keywords: Age-related macular degeneration; bevacizumab; ranibizumab; anti-vascular endothelial growth factor.

1. INTRODUCTION

Age-related macular degeneration (AMD) affects those 50 years and older and causes 1% of visual impairment and 5% of blindness globally [1]. Both bevacizumab (brand name Avastin®) and ranibizumab (brand name Lucentis®) are being use for AMD by ophthalmologists worldwide. However, the intravitreal use of bevacizumab for AMD remains controversial as
the use remains off-label. As described by Jansen [2], “the bevacizumab-ranibizumab debacle illustrates the ethical, policy and legal dilemmas encountered with the off-label use of medication”.

2. CHRONOLOGY OF REGISTRATION OF BEVACIZUMAB AND RANIBIZUMAB

Both bevacizumab and ranibizumab, an anti-vascular endothelial growth factor (VEGF) were developed by Genentech, which was acquired by Roche in 2009. Ranibizumab is marketed by Novartis outside USA. Bevacizumab is a humanised full-length antibody that is derived from the same monoclonal antibody as ranibizumab. Therefore it is likely to recognise the same epitope on all isoforms of VEGF as ranibizumab, but having a different binding affinity. Bevacizumab was first approved by FDA for intravenous use in metastatic colon cancer in 2004 [3]. Ophthalmologist had started using bevacizumab when there were case reports on its efficacy. The obvious efficacy resulted in the rapid adoption in many countries. Ranibizumab was later approved for intravitreal use by FDA for treatment of patients with neovascular (wet) AMD in 2006 [4]. The use of bevacizumab for AMD continues after ranibizumab approval as the price of bevacizumab is 30-50 times cheaper than ranibizumab and more evidence showed the relative efficacy and safety of bevacizumab to ranibizumab. Lack of incentive of marketing intravitreal bevacizumab for AMD use might deter the company for registering the drug for AMD use.

3. HEAD-TO-HEAD COMPARATIVE EFFECTIVENESS TRIAL OF BEVACIZUMAB TO RANIBIZUMAB

As of today, there are several published head-to-head comparative effectiveness trials of bevacizumab to ranibizumab for neovascular AMD. The major trials are Comparison of age related macular degeneration treatment trials (CATT) funded by National Eye Institute in the USA [5,6], the inhibition of VEGF in Age-related choroidal Neovascularisation (IVAN) trial by UK National Institute for Health Research (NIHR) Health Technology Assessment Programme [7,8], Groupe d’Etude Francais Avastin versus Lucentis dans la DMLA neovasculaire (GEFAL) trial in France [9] and Multicentre Anti-VEGF trial in Austria (MANTA) [10]. Both IVAN and CATT had released 2 years results whereas the GEFAL and MANTA trials provided a 1-year result. All CATT, IVAN, GEFAL and MANTA trials were designed as multicentre, prospective and randomised control trial yet the non-inferiority limit for all 4 trials differs slightly. The primary outcome studied was best-corrected visual acuity (BCVA). MANTA trial was powered to detect a difference of 7 letters with 95% confidence, more letters than CATT (5 letters with 99.2% confidence), GEFAL (5 letters with 95% confidence) and IVAN (3.5 letters with 95% confidence). The results from all 4 trials shows that bevacizumab was non-inferior to ranibizumab (Table 1).

4. RESULTS OF LATEST PUBLISHED META-ANALYSIS COMPARING INTRAVITREAL BEVACIZUMAB TO INTRAVITREAL RANIBIZUMAB

In addition to the head-to-head trial, there were several systemic reviews and meta-analysis which showed intravitreal bevacizumab was non inferior to intravitreal ranibizumab in terms of efficacy [11-13]. In terms of safety aspect, it was found that bevacizumab tends to have higher risk of adverse effects as shown in meta-analysis by Wu et al. [11] and the risk of serious systemic events increased by 17% (95% CI 6%-27%, \( P = 0.0042 \)) for bevacizumab treatment in comparison with ranibizumab. Another meta-analysis conducted by Kodjikian et al. [12] found that bevacizumab was associated with a 34% increase in the number of patients with at least one serious systemic adverse event (OR 1.34, 1.08 to 1.66, \( P = 0.01 \), \( I^2 = 0 \% \)). The result was consistent with another meta-analysis conducted by Chen et al which found increase risk of systemic adverse events with bevacizumab [pooled risk ratios comparing the rates of serious systemic adverse events at 1 year and 2 years were slightly in favour of ranibizumab (risk ratio = 1.24, 95% CI, 1.04-1.48, \( P = 0.02 \) and risk ratio = 1.20, 95% CI, 1.05-1.37, \( P = 0.008 \), respectively)], whereas the rates of death, arteriothrombotic events and venous thrombotic events did not differ statistically [13].

5. PROFESSIONAL BODIES STAND ON USING INTRAVITREAL BEVACIZUMAB

5.1 Royal Society of Ophthalmology UK [14]

Based on the latest guidelines issued by the Royal Society of Ophthalmology, UK in 2013 [14], bevacizumab was having similar functional efficacy as ranibizumab. However its unlicensed
use for intraocular purpose need to be highlighted and its prescriber need to convey the “off-label” status to the patient prior to its administration to patient. It was also mentioned in the guidelines that for the licensed anti-VEGF treatment, further research is required into appropriate duration and optimal regimen in terms of frequency of injections as there is lack of evidence on whether less frequent dosing of licensed treatment will achieve the same visual benefit as those in pivotal trials.

Table 1. Head-to-head comparative effectiveness trial of bevacizumab to ranibizumab

<table>
<thead>
<tr>
<th>Name of trial</th>
<th>No. of patients</th>
<th>Study groups</th>
<th>Study result</th>
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</table>
| 1. CATT       | 1208            | • Monthly bevacizumab  
• Monthly ranibizumab  
• PRN bevacizumab  
• PRN ranibizumab | 1 year result [5]  
• Bevacizumab administered monthly was equivalent to ranibizumab administered monthly (8.0 letters gained for bevacizumab vs 8.5 letters gained for ranibizumab).  
• Bevacizumab PRN was equivalent to ranibizumab PRN (5.9 letters gained for bevacizumab vs 6.8 letters gained for ranibizumab).  
• Proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.11% vs 19.0%; \( P=0.04 \)).  
• Rates of death, myocardial infarction and stroke were similar for both group of drug regardless of type of treatment regimen.  
2 year result [6]  
• Ranibizumab and bevacizumab had similar effects on visual acuity (bevacizumab-ranibizumab difference, -1.4 letters, 95% CI -3.7 to 0.8, \( P=0.21 \)).  
• Mean gain in visual acuity was greater for monthly than for PRN regimen (difference, -2.4 letters, 95% CI -4.8 to -0.1, \( P=0.046 \)).  
• Proportion of patients with 1 or more systemic serious adverse events was higher with bevacizumab than ranibizumab (39.9% vs. 31.7%, \( P=0.009 \)). |
| 2. IVAN       | 610             | • Monthly bevacizumab  
• Monthly ranibizumab  
• PRN bevacizumab  
• PRN ranibizumab | 1 year result [7]  
• The comparison of visual acuity at 1 year between bevacizumab and ranibizumab was inconclusive.  
• Visual acuities with monthly regimen and PRN regimen treatment were equivalent.  
• Fewer participants receiving bevacizumab had an arteriothrombotic event or heart
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<td>failure (odds ratio [OR], 0.23; 95% CI, 0.05 to 1.07; (P = 0.03)).</td>
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<td>- There was no difference between drugs in the proportion experiencing a serious systemic adverse event (OR, 1.35; 95% CI, 0.80 to 2.27; (P = 0.25)).</td>
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<td>2 year result [8]</td>
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<td>- Bevacizumab was neither non-inferior nor inferior to ranibizumab. (Mean BCVA difference of bevacizumab and ranibizumab -1.37 letters, 95% CI -3.75 to 1.01; (P=0.26)).</td>
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<td>- Reduction in the frequencies of retreatment resulted in a small loss of efficacy irrespective of drug.</td>
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<td>- Safety was worse when treatment was administered for PRN regimen (Lower mortality with monthly treatment group than PRN treatment group (OR 0.47, 95% CI 0.22-1.03, (P=0.05)) but did not differ by drug group (0.96, 0.46-2.02, (P=0.91)).</td>
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- 3 monthly loading dose of bevacizumab followed by PRN bevacizumab |
- 3 monthly loading dose of ranibizumab followed by PRN ranibizumab |
- Bevacizumab was non inferior to ranibizumab (bevacizumab minus ranibizumab +1.89 letters, \(P=0.39\)). |
- The mean number of injections was 6.8 in bevacizumab group and 6.5 in ranibizumab group. |
- The proportion of patients with serious adverse events was similar in both groups (12.6% in bevacizumab group and 12.1% in the ranibizumab group, \(P=0.88\)). |
- Mean decrease of 95µm for bevacizumab and 107µm for ranibizumab for central subfield macular thickness (\(P=0.27\)). |

4. MANTA [10] 321

- 3 monthly loading dose of bevacizumab followed by PRN bevacizumab |
- Mean increase of 4.9 letters in the bevacizumab group and 4.1 letters in the ranibizumab group (\(P=0.78\)). |
- No statistical difference of
5.2 American Academy of Ophthalmology [15]

American Academy of Ophthalmology recommend the use of both bevacizumab and ranibizumab for age-related macular degeneration. For bevacizumab, the ophthalmologist need to obtain the informed consent from the patient with regards to its off-label use.

6. COUNTRIES EXPERIENCE AND STAND OF USING INTRAVITREAL BEVACIZUMAB AND RANIBIZUMAB FOR AMD

6.1 World Health organization

Bevacizumab was listed in WHO Model List of Essential Medicines in 2013 for ophthalmology use [16]. It was included in the List on the ground of public health need, demonstrated safety and effectiveness and favourable cost-effectiveness [17].

6.2 Malaysia

At the present moment, only ranibizumab is listed in the Ministry of Health Drug Formulary (as of 07/07/2014) for AMD in the public sector. There was evidence of usage of intravitreal bevacizumab in Malaysia but the extent and indication of its use is unknown. Online search for published study which indicate bevacizumab usage in Malaysia setting yield evidence of usage of intravitreal bevacizumab in International Specialist Eye Centre (ISEC) [18], Malaysia National University Hospital [19] and University Malaya Medical Center [20].

6.3 United Kingdom

There were mixed reaction in terms of usage of bevacizumab in the UK. The NHS North East Treatment Advisory Group (NETAG) reported that there will be a significant cost saving of using bevacizumab and the efficacy for both bevacizumab and ranibizumab is comparable.

Hence, bevacizumab was used in NHS North East treatment centres [21]. From the economic analysis conducted by the NETAG, the use of six doses of ranibizumab in the first year will cost £4.766 million per annum. If bevacizumab was used instead the cost would be £274,200, a saving of £4.491 million [21]. If the result of CATT was applied where 1 extra injection was required per annum for bevacizumab, the cost of using bevacizumab is still £4.007 million less than using ranibizumab [21]. On the other hand, the south coast of England (Southampton, Hampshire, Isle of Wight and Portsmouth) cluster of primary care trust discontinued the policy funding of bevacizumab as an alternative treatment for wet AMD after Novartis seek judicial review of the decision [22,23].

6.4 Italy

Recently, the Italian antitrust authorities had fined the two Swiss pharmaceutical companies, Novartis and Roche for a total of $250 million for “colluding to keep doctors from prescribing a relatively inexpensive drug” [24]. The authorities claimed that “the two companies had sought to steer doctors away from Avastin as had been use as off-label for years to channel demand toward the much more expensive Lucentis, through an artificial distinction between the two products by overstating the dangers of Avastin use” [24]. The Italian authority estimated that the addition cost of €45million in 2012 to Italian health service was due to the collusion and this cost might exceed €600m a year in the future [24].

6.5 Thailand

The Thailand’s National List of Essential Medicines Committee announced the inclusion of bevacizumab for the treatment of macular disease in its pharmaceutical benefit package [25]. Based on the comparative effectiveness research study conducted by Health Interventional and Technology Assessment Program (HITAP) [25], it was found that bevacizumab is superior to nonpharmaceutical treatments for acute macular degeneration and
diabetic macular edema but inconclusive for retinal vein occlusion, given the limited difference.

6.6 Australia

Ranibizumab, Vertepronin and Afillercept were reimbursed under Pharmaceutical Benefits Scheme (PBS) for age-related macular degeneration. Due to the off-label use of bevacizumab, it was not reimbursed under PBS [26].

7. CONCLUSION

Based on evidence from head-to-head trials comparing bevacizumab and ranibizumab for AMD, it was found that bevacizumab was non-inferior to ranibizumab in terms of efficacy. However, some studies shows that the use of bevacizumab was associated with an increased risk of developing serious systemic events as compared to ranibizumab. The widespread use of bevacizumab despite its off-label status is due to the significant difference of cost between the two drugs as ranibizumab is 30-50 times more expensive than bevacizumab. Selection of either agents depends on the country viewpoint in terms of public health needs and priority. When cost is the main concern, the country will opt for cheaper yet “off-label” bevacizumab. However, due to legal implication of off-label use, some countries will prefer to choose the drug with licensed indication. If a physician need to prescribe the intravitreal bevacizumab, the “off-label” status of the drug should be conveyed to the patient.

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COMPETING INTERESTS

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