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Mini-Review

Intravitreal Bevacizumab in Neovascular Age-Related Macular Degeneration as First Choice: a New Italian Ruling

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ABSTRACT

Background: Intravitreal vascular endothelial growth factor (VEGF) inhibitors represent the mainstay of neovascular age-related macular degeneration (nAMD) treatment. Although bevacizumab has been the first anti-VEGF used in ophthalmology, it is unlicensed for intraocular use. However, the favourable cost-benefit balance has favoured its widespread use. We aimed to present relevant literature regarding the safety profile and the regulatory issues of intravitreal bevacizumab use.
Methods: In this narrative review we report relevant studies regarding the safety profile of intravitreal bevacizumab. Expert commentary is provided and an overview of the current scenario and possible future directions discussed.
Results: Randomized controlled trials have demonstrated that bevacizumab is not inferior to the licensed anti-VEGF agents showing similar efficacy and safety profiles. However, a significant debate on the regulatory issues of intravitreal bevacizumab used as 'off label' first-line treatment in nAMD still persists. Recently, the Regional Health System of Lombardia in Italy decided to only cover the expenses of bevacizumab, forcing clinicians to use bevacizumab as the first choice in the treatment of nAMD. Issues about the practical implications of this decision are discussed.
Conclusion: The use of intravitreal bevacizumab as first-line therapy in nAMD remains controversial. Many differences in the regulatory aspects still persist among the European countries and sometimes within the same countries, like Italy. Of note the clinical scenario will be modified in future by the introduction of newly developed anti-VEGF agents and anti-VEGF biosimilars.

KEY WORDS

Age-Related Macular Degeneration; Anti-Vascular Endothelial Growth Factor; Drug License Registration; Intravitreal Bevacizumab; Off-Label Use; Randomized Controlled Trial

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INTRODUCTION

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents currently represent the mainstay of neovascular age-related macular degeneration (nAMD) treatment [1-3]. In Europe, there are three available anti-VEGF agents for intravitreal use, namely bevacizumab (Avastin®, Genentech Inc./Roche), ranibizumab (Lucentis®, Genentech Inc./Novartis) and aflibercept (Eylea®, Regeneron/Bayer) [4]. The first evidences of activity in nAMD have been reported with systemic bevacizumab [5], which has been originally approved for the metastatic colorectal cancer and advanced breast cancer treatment [6].

Although bevacizumab has never taken the on label patent for intraocular use, its widespread use in the treatment of nAMD has been encouraged by its favourable cost. Indeed, bevacizumab is by far cheaper

than ranibizumab and aflibercept [7], hence rapidly gained popularity among the ophthalmologists, even after the registration of ranibizumab and aflibercept for intravitreal use in nAMD [8, 9].

In Italy the Ministry of Health is accountable for the Italian National Health System (Sistema Sanitario Nazionale - SSN) planning and for the coordination of regional activities, aimed at guaranteeing the same essential levels of care in all areas of the country. Regions are called to define their own health plans to organize health services delivery within their own territory according to the central government planning [10]. The Italian Medicine Agency (Agenzia Italiana del Farmaco - AIFA) is competent in the regulation of both approved drugs and off-label treatment. In 2018 the European Justice Court judgment expressed no objection to the use of bevacizumab for the treatment of retinal diseases [11]. Following the aforementioned judgement, in July 2019 the Region of Lombardia, one of the wealthiest and populated Italian regions, ruled to reimburse a fixed amount of 55,60 EURO for each injection in patients with nAMD, irrespective of the anti-VEGF agent used [12]. The decision has been supported by the evidence of similarity of the currently available anti-VEGF drugs in terms of safety and efficacy in nAMD, with a remarkable cost effectiveness in favour of bevacizumab [12, 13].

Ophthalmologists are formally free to choose either of the anti-VEGF agents available. However, since 55,60 EURO can only cover the expenses of bevacizumab, this decision has forced hospitals and healthcare organizations in Lombardia to switch to bevacizumab as first choice in nAMD. A few years before this decree in Lombardia, the Italian Regions of Emilia-Romagna and Veneto had been allowed by the AIFA to use bevacizumab for nAMD in public hospitals [14, 15]. However, unlike the current scenario in Lombardia, the clinicians of Emilia-Romagna and Veneto have the option to get the on label anti-VEGF agents (ranibizumab and aflibercept) funded as the first-line treatment in nAMD.

The recent decision of the Regional Health System of Lombardia has led us to briefly review the safety profile of bevacizumab and to give an overview about the pharmacology, regulatory issues and the pros and cons of intravitreal bevacizumab use in nAMD.

METHODS

This is a narrative review based on a PubMed search through April 2020 aimed at reporting relevant literature regarding the safety profile and the regulatory issues of intravitreal bevacizumab use. Reference lists were checked to identify additional relevant studies. Expert commentary is provided and an overview of the current scenario and possible future directions discussed.

DISCUSSION

Pharmacology and Safety Profile

Intravitreal anti-VEGF drugs pass in to the systemic circulation and are able to decrease the plasma-free VEGF [8], theoretically increasing the risk of systemic thromboembolic events [16]. Of note, anti-VEGF molecules containing the antibody fragment crystallizable (Fc) region (bevacizumab and aflibercept) can remain in circulation longer than the anti-VEGF agents without the Fc region (ranibizumab) [8], resulting a longer half-life, slower systemic catabolism and a stronger decrease of plasma-free VEGF.

Several randomized controlled trials (RCTs) such as the Comparison of Age-related macular degeneration Treatments Trials (CATT) study and the alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularization (IVAN) study, have demonstrated that bevacizumab is not inferior to ranibizumab in the treatment of nAMD showing similar efficacy and safety profiles [17-21]. In 2014 a Cochrane systematic review of non-industry sponsored RCTs showed no statistically significant differences in deaths due to thromboembolic events such as stroke or myocardial infarction between bevacizumab and ranibizumab [22].

On the other hand, the risk of thromboembolic events could be underestimated in real life setting compared to RCTs data. Indeed, patients with history of stroke or myocardial infarction are usually excluded from sponsored multicentre clinical trials [16]. Moreover RCTs are designed to primarily assess the efficacy of drugs rather than their safety [16]. Thus, to date it is not possible to definitely answer the question whether there is a definite increased cardiovascular risk of using anti-VEGF agents in such patients who are eligible for treatment. However, pharmacokinetic/pharmacodynamic and safety data reported in both clinical trials and real world studies provide robust evidence that systemic events due to intravitreal injections are very unlikely [23] with no evidence of increased risk of death in patients [24].

At present the vials of bevacizumab are fractioned by the hospital pharmacies under sterile conditions and thereafter sent for the intravitreal use. Conversely, the vials of ranibizumab and aflibercept are prepared by an automated production line acquired directly from the manufacturer. Therefore, concern has been raised about possible microbial contamination during the compounding procedures for bevacizumab, resulting in higher levels of infectious endophthalmitis [25]. However, subsequent large data have showed that the rate of

endophthalmitis with the pharmacy-compounded bevacizumab is not superior to single-use vials of ranibizumab [26]. Knowledge based on scientific evidence must guide our medical decisions and not the marketing status [27]. At present, there is no definite evidence-based reason not to use intravitreal bevacizumab because of systemic safety issues [7, 16] (Table 1).

Table 1: A Summary of Safety Profile of Intravitreal Bevacizumab Use in Ophthalmology

Pharmacology and Safety Profile of Intravitreal Bevacizumab.
Intravitreal anti-VEGF drugs pass into the systemic circulation and are able to decrease the plasma-free VEGF.
RCTs showed no statistically significant differences in mortality rate due to thromboembolic events between bevacizumab and ranibizumab.
CATT and IVAN studies demonstrated that bevacizumab is not inferior to ranibizumab in the treatment of nAMD.
The rate of endophthalmitis with the pharmacy-compounded bevacizumab is not superior to the single-use vials of ranibizumab.

Abbreviations: CATT: Comparison of Age-related macular degeneration Treatments Trials; IVAN: Inhibit VEGF in Age-related choroidal Neovascularization; nAMD: neovascular age-related macular degeneration; RCTs: randomized controlled trials; VEGF: vascular endothelial growth factor.

Regulatory Issues

In spite of the good safety profile, over the past years, the use of bevacizumab as first-line therapy in nAMD has been discouraged by many health authorities and National health systems across the world [7]. Indeed, the prescription of bevacizumab has always been limited in countries other than the United States [28, 29]. However, the increasing demand of anti-VEGF treatment in nAMD with the resulting cost burden has led the European countries to a more liberal attitude on the use of the less expensive bevacizumab [7]. The use of an off-label drug in the presence of on-label drugs is controversial because of its regulatory and legal implications. A simple solution would have been the registration of bevacizumab for intraocular use. Roche and Genentech developed both bevacizumab and ranibizumab, respectively. As far as we know, Roche has never requested the license for intraocular use of bevacizumab.

Over the last decade we have assisted to a significant debate on the use of intravitreal bevacizumab in ophthalmology. In Italy, like in many other European countries, bevacizumab has been extensively used before the introduction of ranibizumab. Indeed, the Italian "off-label law" N° 648/1996 [30] allows the use of off-label drugs in absence of an on-label option and the use of bevacizumab was justified by the evidence that it was safe and more effective than the established treatment of nAMD at that time, namely photodynamic therapy [5, 31]. Once ranibizumab had been marketed and approved for nAMD, in Italy the use of bevacizumab has been at first dismissed, then reintroduced with an annex of the off-label law 648/1996 and thereafter dismissed again by the AIFA in 2012 [32].

Meanwhile, the Italian Competition Authority (Autorità Garante della Concorrenza e del Mercato - AGCM) sentenced against Roche and Novartis, respectively the owners of bevacizumab and ranibizumab, for raising unmotivated concerns about the safety of bevacizumab while promoting the more expensive ranibizumab [33]. AGCM recalled the assessment of the European Medical Agency (EMA) which did not find any greater systemic risk in the intravitreal use of bevacizumab compared to ranibizumab [34]. In 2017, the AIFA has reintroduced intravitreal bevacizumab in the list of the off-label drugs reimbursed by the SSN [35]. In November 2018 the European Court of Justice sentenced that each Country has the authority to allow the use of an off-label drug for social and economic reasons [33, 36, 37] accepting the request submitted by the AIFA in 2017.

On these grounds, in July 2019 the Local Health Authority of Lombardia decided for a massive change, economically introducing bevacizumab as the first-line treatment of nAMD with an authoritative and unprecedented straightforward policy decision in Italy [12]. It has taken a couple of months to see a "massive switch" to bevacizumab for nearly all patients with nAMD in the region.

The Regional Health System of Lombardia tracked the prescription of the intravitreal anti-VEGF agents in Lombardia before and after the decree of July 2019 [12]. Before the decree, ranibizumab, aflibercept and bevacizumab accounted for 63%, 37% and less than 1% of the total number of injections, respectively. In November 2019, with the full application of the decree, the prescription of anti-VEGF drugs significantly changed in favour of bevacizumab as ranibizumab, aflibercept and bevacizumab accounted for 17%, 8,8% and 73,2% of the total number of injections, respectively [38]. Of note, the latter data include anti-VEGF agents prescribed also for conditions other than nAMD, namely diabetic macular edema, macular edema secondary to retinal vein occlusions, and any choroidal neovascularization-associated condition.

Expert Commentary

While this decree in Lombardia will save a large amount of health care funds, it possibly goes against the concept of personalized medicine based on patients individual needs

by limiting the options of the clinicians in the choice of the most appropriate anti-VEGF agent. It is indeed impressive how strong may be the impact of politics, mainly driven by economic considerations, on the clinical decisions and ultimately on the health of patients.

Significant issues have been raised about the practical implications of this decree. First, at present only a limited number of hospital pharmacies in Lombardia provide bevacizumab for intravitreal use. This has led to an overload of these hospitals with an unexpected number of patients who were already under treatment with either ranibizumab or aflibercept in other centers. Second, some patients who poorly respond to one anti-VEGF agent may possibly benefit from switching to another anti-VEGF agent [39, 40]. Clinicians and the Lombardia Region authorities should come to an agreement about the switching criteria to the other anti-VEGFs in case of poor response to bevacizumab.

Current trends and future directions

In the current literature there is little evidence on such a massive switch driven by a policy decision and therefore this scenario may represent an opportunity to collect more information about the clinical course of such patients. We would like to mention the case of Sweden where a switch to bevacizumab was imposed by their health authority. While no significant drop of visual acuity was reported after the switch, 18-19% of patients were found to be non-responder to bevacizumab and switched back to ranibizumab or aflibercept [41]. Different attitudes towards the off-label use of bevacizumab in nAMD across the European Nations have been shown by a recent report [42]; indeed in Europe the use of bevacizumab in nAMD may vary considerably, ranging from non-existent (Switzerland, Hungary, Denmark) to very frequent (Romania, Bulgaria, Finland, Ireland, Netherlands). Moreover, large disparities within single countries, resulting from different organization of the National Health Systems and regional autonomies have been reported [42].

In the United Kingdom, until recent years, the General Medical Council and the National Institute for Health and Care Excellence (NICE) guidelines have not encouraged ophthalmologists to use bevacizumab in nAMD [43]. However, in September 2018, an association of 12 Local Health Authorities of the North England (namely the Clinical Commissioning Groups of the National Health Service) have obtained the legal right to use bevacizumab as the first-line treatment in nAMD [44].

Despite the favourable reports of the EMA about bevacizumab in terms of efficacy, safety and cost profiles, the attitude of the European health authorities about the use of bevacizumab in nAMD is still heterogeneous [42].

It should be noted that in future the patents of ranibizumab and aflibercept will expire and biosimilars molecules will be available for the treatment of nAMD and other retinal diseases and will possibly complicate the current scenario and its regulatory issues [45, 46].

Moreover, a newly developed anti-VEGF agent, brolucizumab (Beovu®, Novartis), has been approved by the U.S. Food and Drug Administration and by the EMA for the treatment of nAMD [47]. The main advantage of Brolucizumab over the other anti-VEGFs would be the longer durability, thus having the potential to reduce the treatment burden [48, 49].

CONCLUSION

After a decade of debate about the use of *on-* and *off-label* drugs, the use of intravitreal bevacizumab as first-line therapy in nAMD remains controversial, in spite of its efficacy and safety profile. Over the last few years, the financial sustainability of the government-funded health care systems of the European countries has been challenged. The health care authorities will play a crucial role in exploring new ways to guarantee an effective therapy for nAMD with affordable costs. In this regard, many differences in the regulatory aspects still persist among the European countries and sometimes within the same countries, like Italy [42]. Approval of new drugs and negotiation of their cost with the pharmaceutical companies will pose additional questions. Finally, the clinical scenario will be modified in future by the introduction of anti-VEGF biosimilars, which have the potential to fill the gap between the on-label and costlier anti-VEGFs and the off-label and cheaper bevacizumab [45, 46].

ETHICAL DECLARATIONS

Ethical Approval: This is a narrative mini review based on other published articles and no need for ethical approval.

Conflict of Interest: None.

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