Influence of unilateral intravitreal bevacizumab injection on the incidence of symptomatic choroidal neovascularization in the fellow eye in patients with neovascular age-related macular degeneration (Review)

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Abstract. Neovascular age-related macular degeneration (neovascular ARMD) represents only 10% of ARMD cases but is responsible, if untreated, for quick and severe central vision loss due to major macular changes. The presence of choroidal neovascularization (CNV) in one eye is associated with an approximately 10% risk of CNV development in the fellow eye each year. Intravitreal anti-VEGF therapy has quickly evolved as the standard treatment in neovascular ARMD in the last decade due to significant anatomical and functional improvements, especially in the early stages. In many reports an improvement in the untreated fellow eye was mentioned and systemic exposure was soon confirmed for all anti-VEGF agents after unilateral intravitreal injection. In particular, bevacizumab intravitreal injection is followed by a consistent reduction of serum VEGF levels and the drug was shown to have the longest serum half-life raising important debates about its safety. Once bevacizumab was detected in the fellow eye of an animal model after unilateral injection, the possible influence on fellow eye conversion rate into neovascular ARMD was questioned. Although comparative studies have not found statistically significant differences between drugs regarding the incidence of symptomatic CNV in the fellow eye during treatment, we observed, on a retrospective 36-month evaluation, a reduced incidence of symptomatic CNV in the fellow eye that might be explained by the consistent systemic exposure of bevacizumab.

Contents

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1. Introduction

Age-related macular degeneration (ARMD) is the leading cause of severe, irreversible central visual loss in elderly people, especially in developed countries (1). The prevalence of ARMD significantly increases after the age of 50 with each decade (2). Also, there is a marked tendency for worldwide increasing incidence. Although neovascular ARMD accounts for only 10% of the cases, its presence is associated with a faster and worse prognosis due to metamorphopsia and significant loss of central vision. Due to their remarkable ability to quickly improve symptoms and also to provide consistent visual recovery, intravitreal administration of different anti-VEGF agents is nowadays the standard treatment for many retinal diseases including neovascular ARMD, diabetic retinopathy, diabetic macular edema, venous occlusions and other retinal disorders (3). Ranibizumab (Lucentis®) and

Aflibercept (Eylea®) are FDA and EMA approved for intravitreal use in neovascular ARMD and recently Brolucizumab (Beovu®) received both approvals for this indication. Although multiple studies have confirmed the comparable efficacy and safety of intravitreal bevacizumab (Avastin®) administration to registered anti-VEGF drugs (4-9), bevacizumab continues to have an off-label status. A recent study evaluating bevacizumab use in 20 European countries showed that a consensus on the ophthalmic off-label use of bevacizumab in Europe has not yet been reached and member states have different approaches (10). Bevacizumab intravitreal injections quota significantly varies in different European countries and even developed economies use bevacizumab after informed consent is obtained. In the USA, the majority of retina specialists are using bevacizumab as the first-line drug (11). Thus, due to its worldwide massive use, mainly related to the significantly lower price, bevacizumab is considered to be the most cost-effective drug for neovascular ARMD (12-15).

2. The current state of knowledge regarding the systemic exposure and the influence of unilateral intravitreal anti-VEGF injection on the fellow eye

As in many retinal diseases, one key problem in neovascular ARMD is the fellow eye involvement. Literature data largely vary on this topic. In clinical trials fellow eye involvement was noted at 22, 24 and 36.3% of patients by 24 months (16-18), regardless of the medication. A recent real-life evaluation reported a 32% fellow eye involvement rate at two years (19). Severe macular changes in the affected eye (larger membranes, more intraretinal fluid) in addition to increased age, female sex and genetic disposition correlate to a higher risk of second eye involvement (18,20). Optical coherence tomography angiography (OCTA) evaluation suggests that the presence of subclinical CNV in fellow-eye is associated with an increased risk of exudation (21,22).

Another key problem is the influence of anti-VEGF treatment in one eye on the fellow eye that has no clinical signs of neovascularization at baseline. Post hoc analysis of some major randomized, double-masked, active-controlled, multicenter clinical trials could not reveal any consistent influence of intravitreal ranibizumab or aflibercept injections on fellow eye conversion rates (17,18). When studying bevacizumab, also, no difference was noted in the first study year (7.2% of patients treated with bevacizumab vs. 7.9% of patients treated with ranibizumab). After 2 years, a difference was noted, although not statistically significant (16.6% of patients treated with bevacizumab vs. 20.6% of patients treated with ranibizumab (23). These results can be explained, at least in part, by the systemic exposure and the significantly longer reduction of VEGF serum levels after intravitreal injections of bevacizumab. A consistent reduction in human serum VEGF levels has been observed after intravitreal injections of all anti-VEGF agents but more prominent after the use of aflibercept and bevacizumab (24,25). Different human studies have focused on establishing the systemic half-life of anti-VEGF agents injected intravitreally (26,27). In the case of ranibizumab, the systemic half-life was estimated at 2 h after one injection and 5.8 days after 3 injections of 0.5 mg. The serum half-life of aflibercept is estimated at 11.4 days after three-monthly intravitreal injections of 2.0 mg while bevacizumab has the longest serum half-life, around 18.7 days, after three intravitreal doses of 1.25 mg. Both aflibercept and bevacizumab manifest systemic drug accumulation between the first three doses while ranibizumab has the quickest bloodstream clearance that does not allow significant systemic accumulation. These findings are confirmed by the IVAN study, one of the most important trials of the last decade. The analysis of serum VEGF levels in patients with neovascular ARMD revealed a more consistent and long-standing VEGF suppression induced by bevacizumab as compared with ranibizumab (reduction of 69% for bevacizumab and 20% for ranibizumab at 1 year, and a reduction of 78% for bevacizumab and 28% for ranibizumab at 2 years) (23).

Fellow eye effects due to systemic exposure of bevacizumab have been reported, in real life, from its very early use in many retinal diseases including proliferative diabetic retinopathy, diabetic macular edema, type 2 idiopathic macular telangiectasia, uveitic cystoid macular edema and retinopathy of prematurity (28-30). A recent publication reports a greater therapeutic effect of unilateral bevacizumab in the fellow eye when compared with the other two anti-VEGF agents (31).

In the particular case of neovascular ARMD there are many reports on clinically significant improvements of the untreated fellow eye after unilateral injections of anti-VEGF agents. They concern visual acuity, fluorescein angiography, and/or central macular thickness as measured by spectral-domain optical coherence tomography (SD-OCT) (32,33). In a prospective, non-randomized trial, patients with unilateral neovascular ARMD were treated with intravitreal injection of ranibizumab or bevacizumab and fellow-eye changes of central retinal artery equivalent (CRAE) and central retinal vein equivalent were measured postoperatively using image analysis software. A significant transient narrowing effect on the CRAE was noted in the fellow non-treated eyes of the bevacizumab group only three days after injection (34). This reaction is supposed to be the consequence of bevacizumab interference with nitric oxide production from vascular endothelial cells (35).

If unilateral intravitreal injections of bevacizumab are influencing the conversion rate of the fellow eye in patients with unilateral neovascular ARMD at baseline is still unknown and there is a lack of literature on this topic. After the study approval by the Ethics Committee of 'Retina Center' Eye Clinic (Iasi, Romania), we performed a retrospective, non-comparative analysis on a consecutive group of patients with unilateral neovascular ARMD at baseline, treated with intravitreal bevacizumab exclusively. Informed consent was obtained from each patient. The patients received 3 monthly intravitreal injections of 1.25 mg/0.05 ml bevacizumab followed by additional injections on a treat and extend basis, as a part of the current treatment protocol in neovascular ARMD at 'Retina Center' Eye Clinic in Iasi.

After reviewing data from 255 patients followed-up for 36 months, we found that symptomatic CNV developed in 5 fellow eyes at 12 months (3.08%), 19 fellow eyes at 24 months (10.55%) and in 29 fellow eyes at 36 months (17.90%). These results are somehow intriguing in view of lower incidence as compared with observational large-scale studies involving other anti-VEGF agents and suggest a possible interference of bevacizumab with the fellow eye conversion rate.

3. Conclusions

Until now, the more substantial systemic exposure of bevacizumab after intravitreal injection as compared with ranibizumab and aflibercept has raised challenging discussions concerning only an increased risk of systemic adverse events (especially cerebrovascular accidents) and the interference with VEGF-dependent physiological processes (especially in newborn babies). It also looks very plausible that long-term unilateral intravitreal injections of bevacizumab in neovascular ARMD could prevent the appearance of symptomatic neovascularization in the fellow eye. Whether or not this intriguing effect is significant will be confirmed by larger, comparative studies.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

DCB and DEB contributed to the design of the study, participated in the entire review process and prepared the manuscript. CIB, AM and CIF contributed to the literature research, and the analysis and critical interpretation of the data. MZ and FB conceived the study and revised the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of 'Retina Center' Eye Clinic (Iasi, Romania) and informed consent was obtained from each patient.

Patient consent for publication

Not applicable.

Competing interests

All the authors declare that they have no competing interests.

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