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Evaluation of the Effect of Intravitreal Injections of Brolucizumab on Ocular Hemodynamics in Patients with Neovascular Form of Age-Related Macular Degeneration

DSc. Prof. Karimova M. H., DSc. Makhkamova D. K., PhD., Abdullaeva S. I., PhD., Zakirkhodjaeva M. A., Rakhimova D. A., Khodjaeva Z. A., Xayrullayeva M. I.

Abstract: Purpose. To study the effect of intravitreal injections of brolucizumab on ocular blood flow in patients with neovascular age-related macular degeneration (AMD).

Methods. 35 patients with wet AMD received intravitreal injections of brolucizumab at a dose of 0,05 ml 120 mg/ml. In all patients, blood flow in the ophthalmic artery (OA), central retinal artery (CRA), medial and lateral posterior short ciliary arteries (PSCA) was studied using color Doppler mapping (CDM) and pulsed Dopplerography. Maximum systolic velocity (Vsyst), end-diastolic blood flow velocity (Vdiast) and resistance index (RI) were recorded before treatment, 1-7 days and 1 month after each injection for 3 months. Results. In patients with wet AMD, before treatment, a significant decrease in Vsyst in the CCCA ($p<0.05$) was revealed, as well as an increase in RI in the CAC and CCCA compared with those indicators in healthy individuals. A reliable effect of intravitreal injections of the drug brolucizumab during an observation period of up to 3 months on the state of blood flow velocity in the vessels of the eye has not been established. Normalization of the peripheral resistance index in the CAC and PCCA system in early period after the 2nd injection of brolucizumab.

Conclusion. Intravitreal injections of brolucizumab for neovascular AMD do not have a negative effect on the hemodynamics of the eye.

Keywords: age-related macular degeneration, neovascular form, ocular hemodynamics, brolucizumab.

Age-related macular degeneration (AMD) is one of the common causes of blindness and visual impairment in patients over 50 years of age in economically developed countries [2, 10]. The prevalence of AMD is 14.4% aged 55 to 64 years, 19.4% - from 65 to 74 years and 36.8% in people over 75 years of age [1, 12]. The recent trend towards increasing life expectancy contributes to an increase in this indicator. There are dry and wet forms of AMD. The wet or neovascular form of AMD is characterized by the development of choroidal neovascularization (CNV) with its various manifestations: edema, detachment of the neuro- and pigment epithelium, hemorrhages, exudates, leading to loss of vision [5, 7].

The development of CNV in AMD is a complex process accompanied by tissue ischemia and inflammation the triggers for the production of vascular endothelial growth factor (VEGF).

Some clinical studies confirm that VEGF plays the most important role in stimulating the growth of pathological vessels and increasing vascular permeability

It is known that one of the main links in the pathogenesis of AMD is primary vascular changes in the choroid, leading to hypoxia with impaired tissue perfusion in the retinal pigment epithelium [1, 8]. In recent years, this hypothesis has been increasingly confirmed by the results of studies that indicate pathological changes in blood circulation in the choroidal and retinal vessels in various clinical forms of AMD according to color doppler mapping (CDM).

The appearance of VEGF inhibitors in the world has made “revolution” in the treatment of neovascular AMD, improving the quality of life of these patients. Currently, VEGF inhibitors demonstrate the best functional results compared to other treatment methods. The effectiveness of intravitreal

administration of brolucizumab in patients with neovascular AMD has been proven in controlled randomized trials.

Despite the significant success of antiangiogenic therapy, a comprehensive assessment of results and the possibility of predicting them remains an urgent task. In addition to assessing the dynamics of visual functions and clinical manifestations in response to anti-VEGF therapy, of particular interest is the study of the effect of angiogenesis inhibitors on the state of ocular hemodynamics.

The purpose of this study was to examine the effect of intravitreal injections of brolucizumab on ocular blood flow in patients with neovascular AMD.

Patients and methods

We examined 35 patients (70 eyes) with the wet form in one eye (35 eyes) and the dry form of AMD in the paired eye (35 eyes) aged from 50 to 75 years (average age 62.5±8.3 years). The criteria for excluding patients from the study were: surgical interventions on the eyes, cardiovascular diseases, and other eye diseases affecting visual functions. The control group consisted of 15 volunteers (30 eyes) of the same age group without pathology of the retina, optic nerve or cardiovascular diseases.

In addition to the traditional ophthalmological examination, all patients underwent fundus photography and optical coherence tomography (OCT). To assess the state of blood flow in the vessels of the eyeball and retrobulbar space, duplex scanning (DS) was used in color Doppler mapping (CDM) and pulse Doppler modes using a multifunctional ultrasound diagnostic device VOLUSON 730 Pro "Kretz" and a linear sensor with a frequency from 10 to 16 MHz. CDC was used to visualize blood flow in the ophthalmic artery (OA), central retinal artery (CRA), medial and lateral posterior short ciliary arteries (PSCA).

Identification of vascular branches in the retrobulbar space was carried out according to the expected anatomical passage and direction of blood flow. The flow towards the sensor was indicated in red, and from the sensor - in blue. The direction of blood flow was also determined by the location of the Doppler wave above or below the isoline. Using Doppler spectral analysis, pulsatile arterial blood flow and more continuous or minimally pulsating venous blood flow were identified. By moving the control volume marker cursor, Doppler information was selectively obtained at a certain point in the vessel.

The Doppler frequency shift spectrum (DSDS) was recorded and the main quantitative indicators of blood flow were determined: maximum systolic velocity (Vsyst), end-diastolic velocity (Vdiast) and resistance index or peripheral resistance (RI). Blood flow parameters in one vessel were measured three times, choosing the optimal value. All ultrasound examinations were performed by one specialist at the same time of day (from 10.00 to 15.00).

All studies were carried out before treatment, as well as again 1-7 days and 1 month after each injection.

Treatment of the wet form of AMD included 3 intravitreal injections of brolucizumab (Lucentis) at a dose of 0.5 mg (0.05 ml), carried out according to standard techniques. The observation period was 3 months.

Statistical analysis of the data was carried out using the Excel-7.0 and Bio-Stat computer programs (Microsoft/Windows-XP). Linear values were compared using Student's t test, nonlinear values were compared using Pearson's $\chi 2$ test, and in case of a small sample, Fisher's exact test was used. The difference was considered significant at $p<0.05$.

Results

The results of a study of ocular blood flow indicators in patients with wet AMD before treatment revealed a significant decrease in Vsyst in the ACCA ($p<0.05$), as well as an increase in RI in the CAC and ACCA compared with the same indicators in the control group. In eyes with dry AMD, a significant decrease in Vsyst was observed in the HA, CAC, and CCCA. An increase in RI was

recorded in all studied vessels; a statistically significant increase in this indicator was noted in the GA ($p<0.05$)

Analysis of the results of a study of hemodynamic parameters during intravitreal injections of brolucizumab did not reveal changes in Vsyst in the arteries of the HA, CAC, and CCCA. There was only a weak tendency towards an increase in this indicator in the GA by the end of the 3rd month of observation. The results of the study of RI in GA showed a short-term statistically insignificant increase in this indicator 1-7 days after the first injection, followed by its decrease by the end of 1 month. In the early stages after the second injection (after 1-7 days), RI decreased, on average, to 0.69 ± 0.02 and remained at this level throughout the entire observation period.

Similar changes in RI occurred in CAC and CCCA. There was a normalization of RI in these vessels 1 month after the 1st injection (0.70±0.01 and 0.65±0.02, respectively) and a pronounced decrease 1-7 days after the 2nd injection (0 .63±0.02 and 0.59±0.02, respectively). 1 month after the 2nd injection, a statistically insignificant increase in RI in the CCCA was observed (0.67±0.02, $p>0.05$).

1-7 days after the 3rd injection, a slight decrease in this indicator was recorded in the CAC ($p>0.05$) and more pronounced in the CCCA ($p<0.05$). By the end of the observation period, RI increased, but remained below the initial level.

A dynamic study of hemodynamics in eyes with dry AMD did not reveal statistically significant deviations in ocular blood flow parameters during treatment with brolucizumab in the fellow eye with wet AMD.

When analyzing the clinical material, it was found that a positive result in the treatment of wet AMD was achieved in 91.4% of cases (32 eyes). Of these, in 24 eyes (75%), anti-VEGF therapy was accompanied by an increase in visual functions associated with the resorption of macular edema, hemorrhages, detachment of the pigment epithelium and/or neuroepithelium. In 25% of cases, there was a decrease in exudative manifestations in the fundus without an increase in initial visual acuity; visual functions were stable throughout the observation period.

The remaining 3 patients (3 eyes, 8.6%) experienced deterioration in visual function during intravitreal injections of brolucizumab. Decreased vision was associated with the formation of a rough fibroglial scar in the central zone.

With a comparative assessment of hemodynamic parameters and visual functions, it becomes obvious that with the positive effect of intravitreal administration of brolucizumab, there is an improvement in the perfusion of retinal and choroidal blood flow (increased Vsyst in the CAC and CCCA and normalization of RI in these vessels.

Discussion

In recent years, a number of clinical randomized controlled studies have shown that intravitreal administration of brolucizumab is an effective treatment for neovascular AMD [7, 11]. Particular attention in these studies was paid to assessing the development of cardiovascular complications (myocardial infarction, cerebrovascular disorders, arterial hypertension), which showed the safety of the use of brolucizumab.

In addition to the systemic effect of anti-VEGF drugs, their effect on regional ocular blood flow was studied. The literature describes cases of occlusion of the central nervous system after injection of brolucizumab, but a reliable relationship between these phenomena has not been established .

Thanks to color circulation and pulsed Doppler sonography, we obtain the necessary information about the linear velocity of blood flow (maximum systolic and end-diastolic) at any point in the vessel and the state of vasoresistance. This method was chosen and used by us to assess the effect of brolucizumab on ocular blood flow.

Conclusion

Thus, our study demonstrated the absence of a significant effect of intravitreal injections of the drug brolucizumab during an observation period of up to 3 months on the state of ocular hemodynamics.

Normalization of the peripheral resistance index in the CAC and PCCA system was shown in the early period after the 2nd injection of brolucizumab. The absence of significant changes in the maximum systolic blood flow velocity and the decrease in elevated values of the peripheral resistance index in the CAC and PCCA after the administration of brolucizumab may indicate the absence of circulatory disorders in the retinal and choroidal vessels and the normalization of vasoresistance against the background antiangiogenic therapy.

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