https://doi.org/10.31288/oftalmolzh202432832

Short-term efficacy of a monoclonal antibody fragment (brolucizumab) for treating neovascular age-related macular degeneration

Yusupov A. F., Karimova M. Kh., Djamalova S. A., Makhkamova D. K., Abdullaeva S. I., Zakirkhodjaeva M. A., Khodjaeva Z. A., Rakhimova D. A.

Republican Specialized Scientific and Practical Medical Center for Eye Microsurgery

Tashkent (Uzbekistan)

Aim. *To evaluate the short-term efficacy of using a monoclonal antibody fragment (Brolucizumab) for treating neovascular age-related macular degeneration, depending on the morphometric parameters of the retina.*

Methods. *This study included 48 patients (60 eyes) diagnosed with neovascular age-related macular degeneration (nAMD). The observation period was 6 months. Brolucizumab was administered intravitreally at a dose of 6 mg (0.05 ml, 120 mg/ ml) once a month consistently for 3-4 months. Depending on the morphometric parameters, the retina patients were divided into three main groups.*

Results. *A pronounced clinical and morphological response was achieved after the first injection of Brolucizumab, and positive dynamics were observed throughout the entire observation period.*

Conclusions. *The use of the drug Brolucizumab significantly improves the visual functions of patients with neovascular AMD, as well as the morphological state of the retina in short-term follow-up, regardless of the initial morphometric characteristics of the retina, which allows not only to maintain but also to improve visual acuity and prevent blindness and visual disability in patients.*

Key words:

age-related macular degeneration, neovascularization, optical coherence tomography, brolucizumab, intravitreal injection

Introduction

The main cause of vision loss in patients older than 60 years is neovascular age-related macular degeneration (AMD) [1, 2]. The neovascular form of AMD is characterized by rapid progression, leading to irreversible vision loss (within a year), and the therapeutic window for starting treatment is 12 months. A factor in the development of the wet form of AMD is the increased formation of a protein, vascular endothelial growth factor (VEGF-A).

Under hypoxic conditions, this factor triggers the formation of new pathological vessels under the macula. Because of the defective walls of such vessels, plasma and blood cells escape into the adjacent retinal tissue, which leads to local retinal detachment and the inevitable death of its photoreceptors – rods and cones [3, 4].

Aim. To evaluate the short-term efficacy of using a monoclonal antibody fragment (Brolucizumab) for treating neovascular age-related macular degeneration, depending on the morphometric parameters of the retina.

Materials and methods

Clinical studies were conducted at the Republican Specialized Scientific and Practical Medical Center for Eye Microsurgery. The study included 48 patients (60 eyes) diagnosed with neovascular age-related macular degeneration (nAMD). There were 31 men (65%) and 17 women (35%). The age of the patients ranged from 50 to 70 years, with an average of 61±3.2 years. To conduct the scientific research, according to the Declaration of Helsinki, the Ethics Commission for Medical Research of the EiPK of the Republic of Uzbekistan was approved. In addition, for inclusion in the research work, the voluntary informed consent of the patients was obtained.

The criterion for including patients in the study was the presence of neovascular AMD.

Exclusion criteria from this study were: the presence of a dry form of AMD, diabetic retinopathy, inflammatory and degenerative diseases of the organ of vision, traumatic injuries to the eyeball, autoimmune and syndromic diseases of the eye, congenital anomalies of the organ of vision, and hypersensitivity to brolucizumab or any other component of the drug. All patients underwent standard ophthalmological examinations: visometry, kerotorefractometry, tonometry, computer perimetry, biomicro-ophthalmoscopy, B-scan, and optical coherence tomography with angiography. The observation period was 6 months.

To assess the morphometric parameters of the retina, an optical coherence tomograph with angiography DRI OCT TOPCON Triton plus (Ver. 10.13) was used. Optical coherence tomography included obtaining a macular map with further extraction of indicators of central retinal thickness (CRT). In addition, the presence of any type of fluid, fluid under retinal pigment epithelium (RPE) or intraretinal fluid (IRF), was determined by reviewing all structural

scans of the macular map. IRF was defined as the presence of hyporeflective round cavities in the neurosensory retina on at least one cross-sectional scan. IRF was defined as the hyporeflective space between the neurosensory retina and RPE on at least one cross-sectional scan. Fluid under the RPE was defined as the hyporeflective space between Bruch's membrane and the RPE.

Brolucizumab was used as an anti-VEGF drug (Vsiqq, Novartis, Switzerland). Brolucizumab was administered intravitreally at a dose of 6 mg (0.05 ml, 120 mg/ ml) once a month consistently for 3-4 months.

The recommended dose of the drug is 6 mg (0.05 ml of solution); the first 3 doses are administered as an intravitreal injection 4 weeks apart (monthly). Patients were monitored every 4 weeks after IVI. At the same time, the effectiveness of treatment was assessed based on OCT data.

After three monthly injections, based on visual acuity and morphometric parameters of the retina, the intervals between subsequent injections were selected individually. At 24 weeks (6 months) after the initiation of therapy, disease activity was assessed. In patients with no evidence of disease activity, intravitreal drug administration was performed every 12 weeks. In patients with signs of disease activity, the drug was administered every 4 weeks and then every 8 weeks until the process stabilized.

Depending on the morphometric parameters of the retina, patients were divided into three main groups. Group I consisted of 16 patients (16 eyes). This group consisted of patients in whom the increase in average retinal thickness was in the range of 400-495 microns, and the prevalence of the pathological process was in the range of 1-3 papillo diameters (PD). Group II consisted of 15 patients (25 eyes). In patients, the increase in average retinal thickness was in the range of 500-545 μm, and the prevalence of the pathological process was in the range of 2-3 PD. The III group included 17 patients (19 eyes). This group consisted of patients in whom intraretinal edema was the highest and most extensive, while the increase in average retinal thickness was in the range of 550-600 μm, and the prevalence of the pathological process was in the range of 3-4 PD or more.

For statistical data processing, the MedCalc 18.4.1 software package (MedCalc Software, Belgium) was used. Data are presented as mean±standard deviation. One-way analysis of variance (ANOVA) with repetitions was used to assess the statistical significance of differences in VA before treatment and after 3 injections. The difference was considered statistically significant at $p<0.05$.

Results

Results.

At the first stage, 4 weeks after the introduction of the IVI, short-term results in all three groups showed an improvement in vision and morphometric parameters in dynamics.

Thus, the visual acuity of patients in the first group before treatment was on average 0.13±0.05, and the retinal thickness in the macular area was 400-495 microns (Fig. 1, 3). At 4 weeks after drug administration, visual acuity in these patients improved by 33.8% compared with baseline data and amounted to 0.44, and retinal thickness decreased by 53.9% compared with baseline data and amounted to 231.2±9.1 ($p<0.05$) μm compared to the primary data (Fig. 2, 4). The visual acuity of patients in the second group before treatment was on average 0.11±0.05, and the retinal thickness in the macular region was 500-545 microns. At 4 weeks after drug administration, visual acuity in these patients improved by 22.9% and amounted to 0.48, and retinal thickness decreased by 46% to 238.2±11.3 ($p<0.05$) μm compared to the primary data. In patients in the third group, visual acuity before treatment was on average 0.08, and the retinal thickness in the macular area was 587 mi-

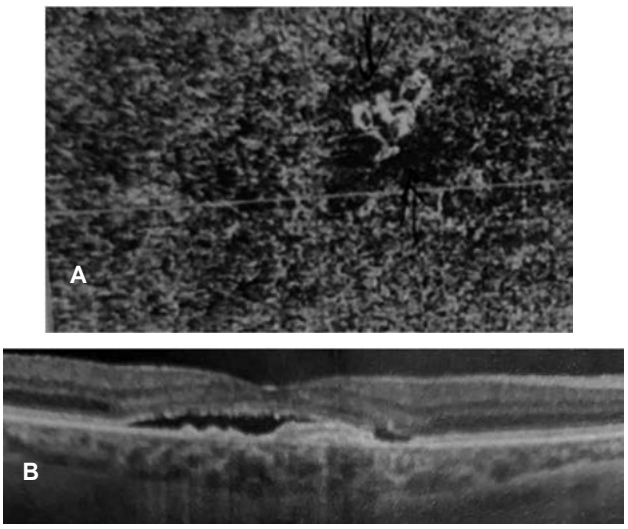


Fig. 1. Results of OCT angiography before anti-VEGF therapy. A – En-Face scan. B – transverse scan. The patient's visual acuity was OD 0.09 with correction of 0.2.

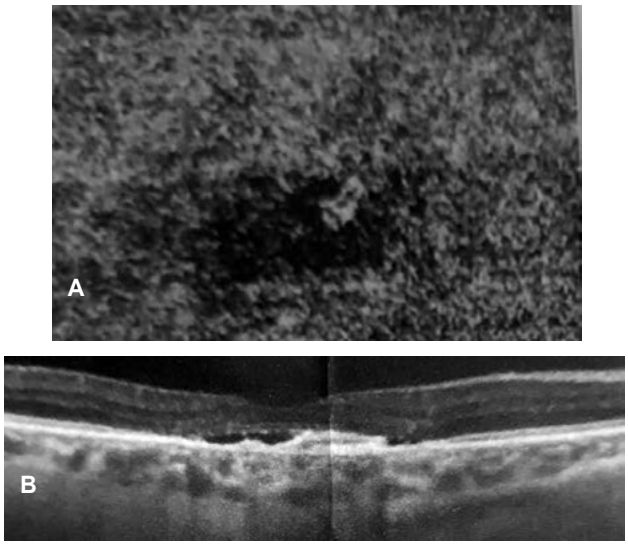


Fig. 2. Results of OCT angiography after 4 weeks of anti-VEGF therapy. A – En-Face scan. B – transverse scan. The patient's visual acuity was OD 0.02 with correction of 0.4.

crons. At 4 weeks after drug administration, visual acuity in these patients improved by 63.7% and amounted to 0.51, and retinal thickness decreased by 37% and amounted to 218.2±12.3 μm ($p<0.05$) compared with the primary data (Table 1).

Groups 1 and 2 included patients who, for various reasons (health status, family circumstances, patient noncompliance with treatment, financial difficulties) were unable to receive the required 3 monthly injections (Fig. 6, 7). Group 3 included patients who received all three loading doses of the drug (Fig. 5).

Table 1. Visual acuity and the average retinal thickness of the patients (4-week follow-up visits)

	Groups	1st time	4 weeks
Visus	1st	0.13±0.05	0.44±0.06*
	2nd	0.11±0.06	0.48±0.07*
	3rd	0.08±0.04	0.51±0.05*
Average retinal thickness, μm	1st	428.2±11.3	231.2±9.1*
	2nd	513.2±21.1	238.2±11.3*
	3rd	587.2± 17.3	218.2±123*

* Statistical significance was $p<0.05$

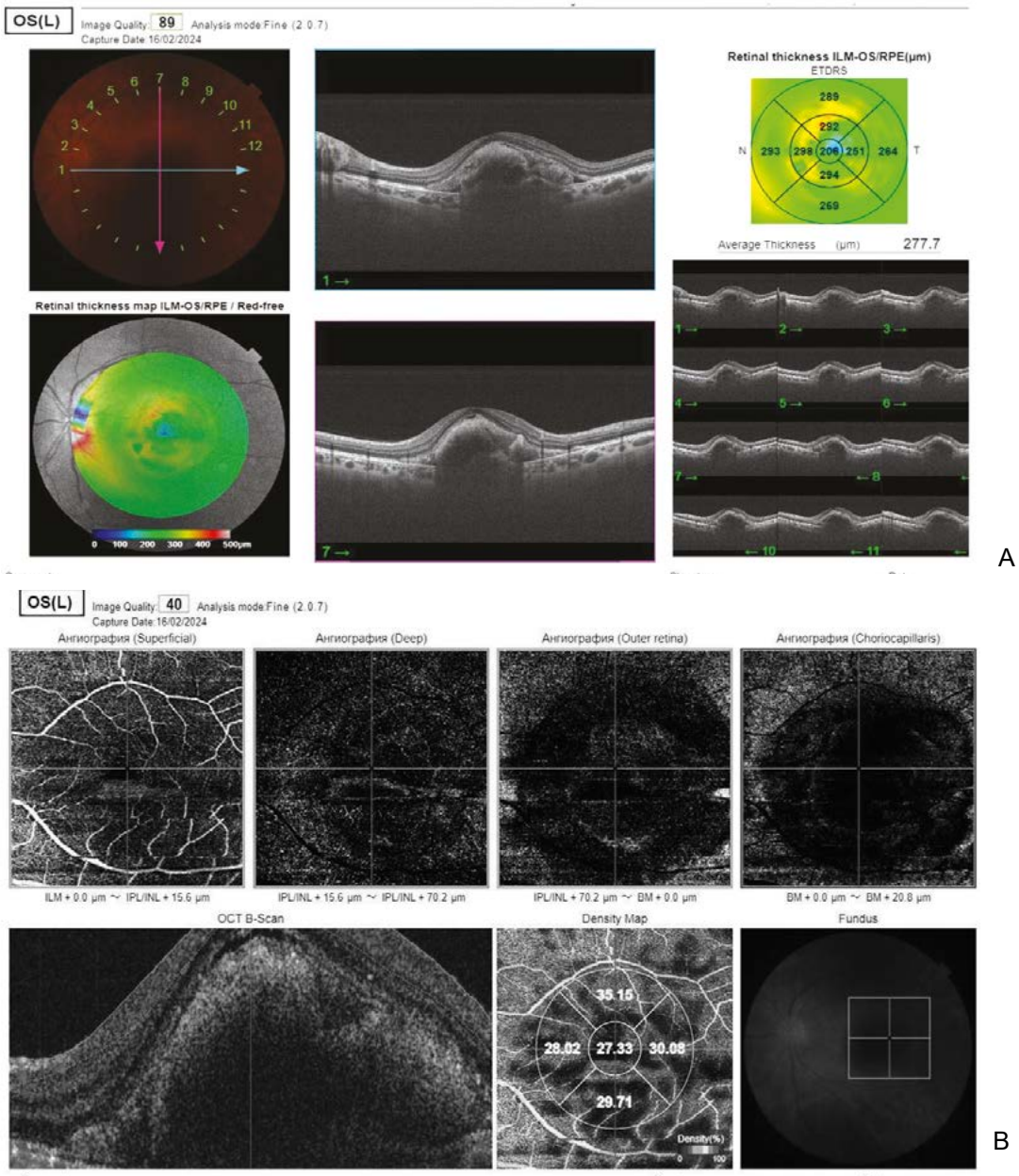


Fig. 7. Results of OCT angiography after 1 dose of anti-VEGF therapy after 44 weeks. A–3D macula scan. B–transverse scan. OCT data of a patient in group 1. The image was registered 44 weeks after anti-VEGF. After receiving the first loading dose of anti-VEGF therapy, the patient did not come for examinations for 11 months due to family reasons.

Table 2. Visual acuity and the average retinal thickness of the patients in group 3 (before treatment, 4, 8, 12 and 24-week follow-up visits)

3rd group	1st time	4 weeks	8 weeks	12 weeks	24 weeks
Visus	0.08±0.04	0.51±0.05*	0.65±0.07*	0.6±0.08*	0.56±0.04*
Average retinal thickness, μm	587.2± 17.3	218.2±123*	217.4±6.3*	214.3±5.3*	212.2±10.8*

* Statistical significance was p<0.05 compared to the primary data.

At the next stage of the study, the dynamics of visual acuity and retinal thickness in patients in group 3 were assessed during a 24-week follow-up period.

The study revealed that a pronounced clinical and morphological response was achieved after the first injection of Brolucizumab in 3rd group, and then positive dynamics were observed throughout the entire observation period (Table 2).

Discussion

Brolucizumab received registration approval for treating patients with nAMD based on the results of the phase 3 global comparative clinical trials HAWK and HARRIER. Brolucizumab offers physicians an important anti-VEGF therapy in their treatment arsenal, which may be useful in preventing and addressing the unmet needs and challenges that plague patients and health care providers. It provides a selection of ideas, recommendations, and resources to help public healthcare providers support all ophthalmic healthcare providers (OPHs) with the tools they need to deliver brolucizumab and local services in a timely and predictable manner [12]

In summary, this conclusion of real-world data shows the effectiveness of brolucizumab in clinical practice in terms of visual acuity, IRF, and SRF improvements in patients with nAMD who were previously treated with anti-VEGF. In addition, the reduction of disease activity in the eyes of patients with the anti-VEGF switch was manifested by lengthening treatment intervals. These observations are consistent with the key tests in the brolucizumab development program. Doctors have probably learned more about how to manage potential risks [13]

In conclusion, retinal fluid is one of the parameters used to measure disease activity in nAMD, and the treatment goals for nAMD include drying the affected retina by inhibiting new blood vessels leaking fluid and improving or maintaining visual acuity. Brolucizumab may be an option for patients who have persistent fluid retention despite receiving current treatment for AMD. The clinical trial data reviewed in this report demonstrated that brolucizumab treatment achieved greater fluid resolution than aflibercept. The ongoing MERLIN trial will provide additional information on the difficult-to-treat patients with persistent fluid. The high solubility of brolucizumab allows for the delivery of more drug per IVT injection, with the potential for better tissue penetration. Brolucizumab also has a low systemic exposure, which is potentially associated with lower systemic adverse effects. Further review of the HAWK and HARRIER data, as well as ongoing clinical trials in nAMD, diabetic macular edema, and retinal vein occlusion, will provide additional evidence for brolucizumab, offering physicians the information they need to make informed decisions about the most appropriate anti-VEGF agent for their patients. [14]

According to the results of our study, despite the short observation period and the small number of intravitreal injections of Brolucizumab performed, after 4 weeks, patients of all groups demonstrated a significant improvement in anatomical and functional indicators (visual acuity and retinal thickness), regardless of the initial morphometric characteristics of the retina, which is fully consistent with previously obtained results in foreign multicenter studies.

Thus, it was found that, regardless of the initial morphometric parameters, after IVI Brolucizumab in the short-term period after 4 weeks of observation, visual acuity and morphometric parameters in patients of all 3 groups improved, and these results persisted for up to 8 weeks.

Because Groups 1 and 2 did not receive the required 3 loading doses, it was not possible to compare data at 8, 12, and 24 weeks.

At the same time, in patients in group 3 who received all three planned loading doses and were under the control of an ophthalmologist, visual acuity and retinal thickness were within 218 μm compared with baseline. This shows that the administration of all necessary planned doses of IVI in a timely manner, as well as monitoring of the pathological process with the help of timely OCT, is a necessary factor for the adequate management of patients with neovascular AMD, which contributes to the stabilization of the disease course. In patients of the 3rd group, who received all three necessary doses of the drug and were also under observation, there was an improvement in visual indicators and the condition of the retina with stabilization of the pathological process. This circumstance indicates the need to perform a full course of IVI according to the indications, followed by a transition to observation and control of the pathological process. To prevent the occurrence of such conditions, it is necessary to achieve an adequate understanding of the seriousness of the patient's condition, increase adherence to therapy, and also make a proposal to higher state bodies to include anti-VEGF drugs in the list of necessary medicines provided by the state.

Thus, the use of the drug Brolucizumab significantly improves the visual functions of patients with neovascular AMD, as well as the morphological state of the retina in

this pathology, which allows not only to maintain but also to improve visual acuity and prevent blindness and visual disability in patients.

Thus, our results prove the need for further research in this group of patients, as well as the likely benefits of early complete suppression of disease activity compared with suppression of activity after a period of relative resistance to previous antiangiogenic treatment.

References

1. **Nguyen QD, Das A, Do DV. et al.** Brolucizumab: Evolution Through Preclinical and Clinical Studies and the Implications for the Management of Neovascular Age-Related Macular Degeneration. Ophthalmology. 2020;127:963-976.
2. **Dugel PU, Koh A, Ogura Y. et al.** HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology. 2020;127:72-84.
3. **Dugel PU, Singh SR, Koh A. et al.** HAWK and HARRIER: 96-Week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology. 2021;128:89-99.
4. **Colijn JM, Buitendijk GHS, Prokofyeva E, Alves D, Cachulo ML, Khawaja AP, et al.** Prevalence of age-related macular degeneration in Europe: the past and the future. Ophthalmology. 2017;124:1753–63.
5. **Daien V, Finger RP, Talks JS, Mitchell P, Wong TY, Sakamoto T, et al.** Evolution of treatment paradigms in neovascular age-related macular degeneration: a review of real-world evidence. Br J Ophthalmol. 2021;105:1475–79.
6. **Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al.** Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1419–31.
7. **Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, et al.** Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012;119:2537–48.
8. **Mousa SA, Mousa SS**. Current status of vascular endothelial growth factor inhibition in age-related macular degeneration. BioDrugs. 2010;24:183–94.
9. **Schmidt-Erfurth U, Chong V, Loewenstein A, Larsen M, Souied E, Schlingemann R, et al.** Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). Br J Ophthalmol. 2014;98:1144–67.
10. **Research G, Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, et al.** Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012;119:1388–98.
11. **Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Culliford LA, et al.** Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet. 2013;382:1258–67.
12. **Pearce, I., Amoaku, W., Bailey, C. et al.** The changing landscape for the management of patients with neovascular AMD: brolucizumab in clinical practice. Eye. 2022;36, 1725–1734 .
13. **Caroline R. Baumal, Torben Lykke Sørensen et al.** Efficacy and safety of brolucizumab in age-related macular degeneration: A systematic review of real-world studies. 2022.
14. **Quan Dong Nguyen et al**. Brolucizumab: Evolution through Preclinical and Clinical Studies and the Implications for the Management of Neovascular Age-Related Macular Degeneration Ophthalmology. July 2020; 127(7):963-976.

Disclosures

Received: 05.02.2024

Accepted: 03.06.2024

Corresponding author: *Khodjaeva Zilolakhon Anvarovna - Khodjayevaz@gmail.com*

Author's contribution: *Data collection and analysis, Writing – original draft; ZAR: Data collection and analysis, Formal Analysis, Writing – review & editing; AON: Data collection and analysis, Writing – original draft; MMU: Conceptualization, Analysis, Project Administration, Writing – review & editing. All authors have read and approved the final manuscript.*

Funding sources: *No financial support was received for this study.*

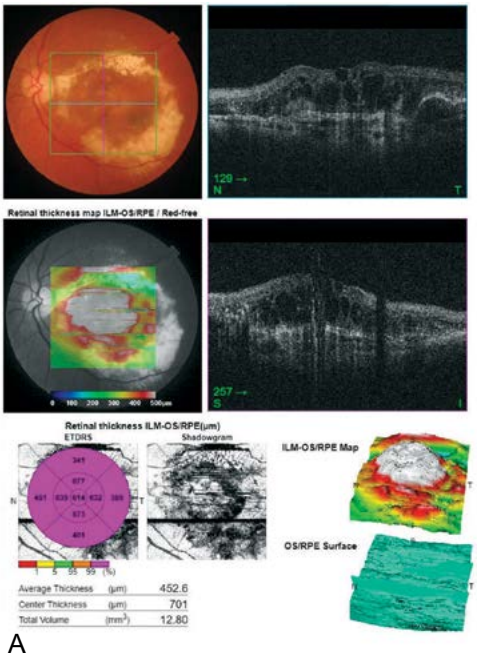
Conflict of interest: *The authors have no conflicts of interest to declare.*

Disclaimer: *The opinions expressed in this article are those of the authors and do not reflect the official position of the institution.*

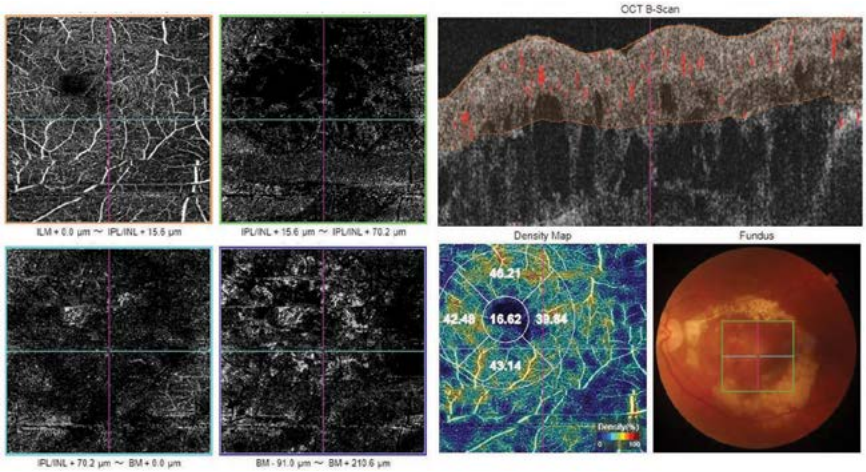
Abbreviations: *anti-VEGF – anti-vascular endothelial growth factor; AMD – age-related macular degeneration; N-AMD – neovascular age-related macular degeneration; RPE – retinal pigment epithelium; IRF – intraretinal fluid, MV – macular volume; CRT – central retinal thickness; SRF – subretinal fluid; IVI – intravitreal injection*

.

Figures to article Yusupov A. F. et al. «Short-term efficacy of a monoclonal antibody fragment (brolucizumab) for treating neovascular age-related macular degeneration»

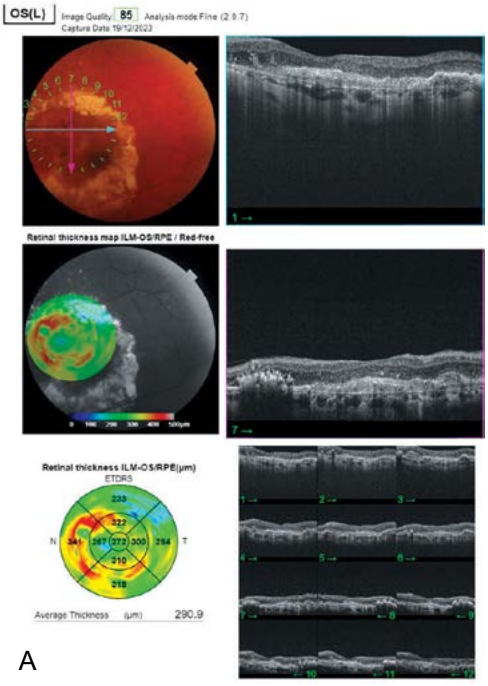


A

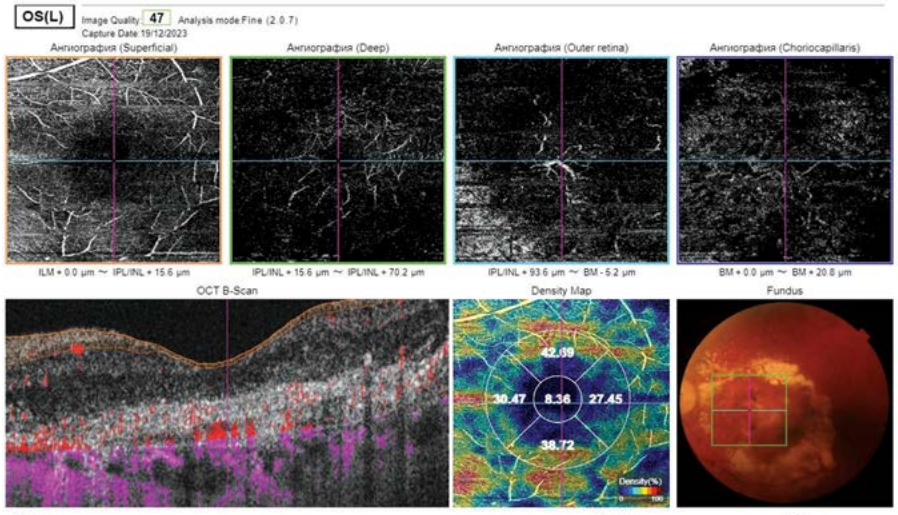


B

Fig. 3. Results of OCT angiography before anti-VEGF therapy. A – 3D macula scan B – transverse scan.



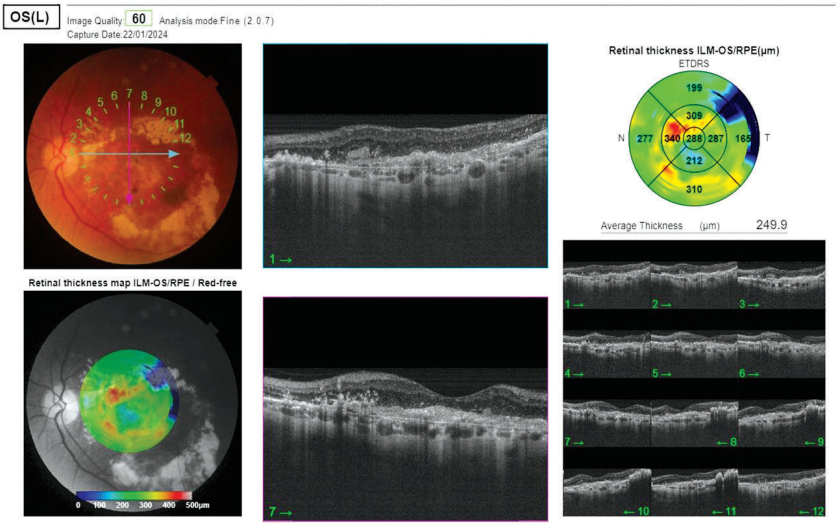
A



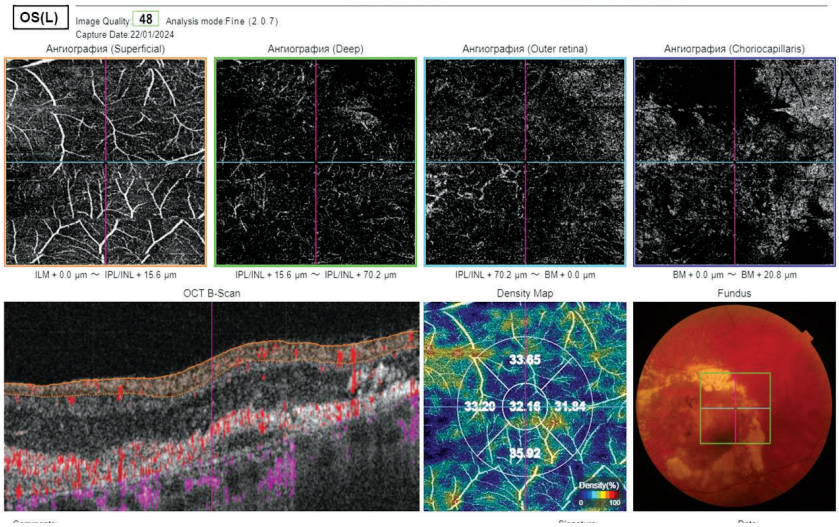
B

Fig. 4. Results of OCT angiography after 4 weeks of anti-VEGF therapy. A – 3D macula scan. B – transverse scan.

Figures to article Yusupov A. F. et al. «Short-term efficacy of a monoclonal antibody fragment (brolucizumab) for treating neovascular age-related macular degeneration»

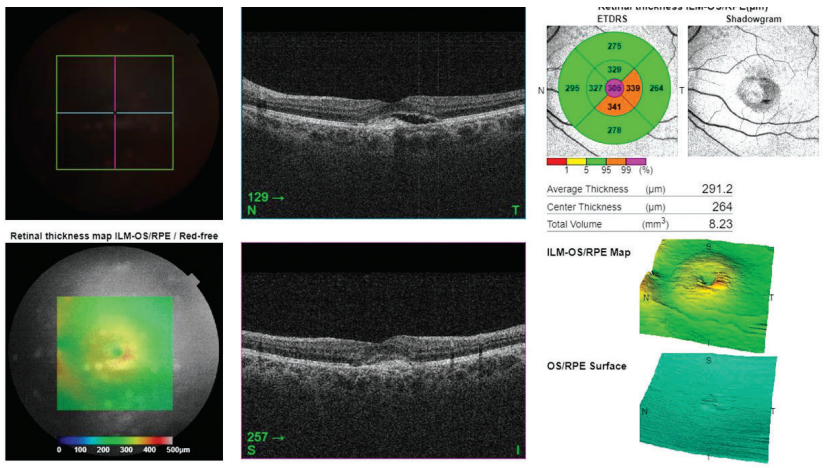


A

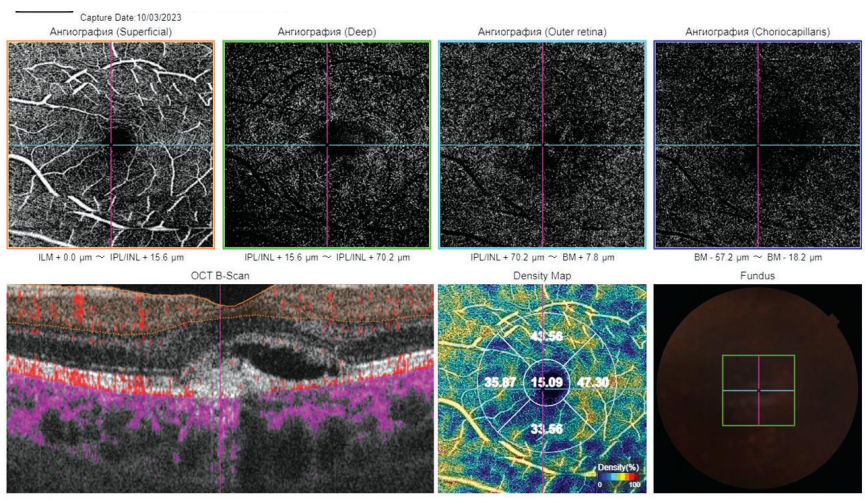


B

Fig. 5. Results of OCT angiography 4 weeks after the third loading dose of anti-VEGF therapy. A 3D macula scan. B is a transverse scan/



A



B

Fig. 6. Results of OCT angiography before anti-VEGF therapy. A 3D macula scan B – transverse scan. OCT data of a patient in group 1. The picture was registered before anti-VEGF.