



DOI: 10.14744/eer.2025.49389
Eur Eye Res 2025;5(3):216–223

EUROPEAN
EYE
RESEARCH

ORIGINAL ARTICLE

Impact of repeated anti-VEGF injections on the corneal nerve plexus in patients with Wet-AMD

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Abstract

Purpose: The study aims to evaluate the effects of anti-vascular endothelial growth factor (anti-VEGF) treatment on corneal nerve morphology and ocular surface health in patients with unilateral wet age-related macular degeneration (AMD).

Methods: The study included 48 patients who received at least three unilateral intravitreal anti-VEGF injections for wet AMD and 25 subjects who were healthy. Corneal nerve morphology was assessed using in vivo confocal microscopy, and ocular surface health by tear film parameters and ocular surface disease index scores. The effects of different anti-VEGF agents (bevacizumab, ranibizumab, and aflibercept) were also compared.

Results: The results showed a marked decline in corneal nerve fiber width (CNFW) in anti-VEGF-treated eyes compared to untreated eyes and healthy control eyes. However, no notable discrepancies in other corneal nerve parameters, tear film parameters, and corneal sensitivity were found between treated, untreated eyes, and healthy control eyes. Furthermore, no statistically significant change was noted between the effects of different anti-VEGF agents on corneal nerves.

Conclusion: Anti-VEGF treatment may affect corneal nerve structure, as indicated by a decrease in CNFW, but does not necessarily lead to changes in corneal sensitivity and tear film parameters. The results of the study suggest that anti-VEGF treatment appears to be safe in terms of its effects on corneal nerves, but further research, especially longitudinal studies, are required to validate these findings.

Keywords: Age-related macular degeneration; anti-vascular endothelial growth factor; subbasal corneal nerve fiber plexus.

Age-related macular degeneration (AMD) is a major worldwide concern in the domain of ocular health, accounting for a substantial proportion of vision loss among individuals aged 50 and above.^[1,2] The etiology of wet-AMD involves hyperactivation of the vascular endothelial growth factor (VEGF) signaling cascade.^[3] In recent years, anti-VEGF agents have become an effective

option for the management of wet-AMD.^[4] However, there have been reports of side effects of anti-VEGF therapy and its effects on retinal nerve fibers,^[5] particularly corneal nerves.^[6]

This treatment is central to the management of wet AMD, though some reports have highlighted potential adverse effects on the ocular surface, including ocular surface



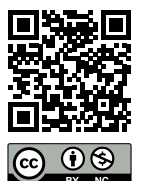
Cite this article as: Guzel E, Erkilic K, Sener H, Polat OA, Unlu M, Ozer F, et al. Impact of repeated anti-VEGF injections on the corneal nerve plexus in patients with Wet-AMD. Eur Eye Res 2025;5(3):216–223.

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Submitted Date: 18.01.2025 **Revised Date:** 28.05.2025 **Accepted Date:** 23.06.2025 **Available Online Date:** 17.12.2025

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irritation, corneal epithelial cell toxicity, decreased corneal nerve fiber density, corneal sensitivity, as well as a decreased ocular surface score index.^[7,8] Consequently, there are few studies on its potential effect on the morphological properties of corneal nerves.

The focal point of the study was to gauge the consequences of anti-VEGF therapy in patients diagnosed with unilateral wet AMD. In particular, we aimed to compare the morphological characteristics of the corneal nerves in treated and untreated eyes and healthy control eyes. In addition, we aimed to investigate the differences in a number of ocular surface health indices between eyes that received anti-VEGF treatment and those that did not.

Materials and Methods

The Local Ethics Committee at Erciyes University approved the research protocol (No: 2023/648, date: October 04, 2023). The research was conducted in accordance with the principles outlined in the Helsinki Declaration. All individuals provided verbal informed consent before participating in the study.

Patient Eligibility

The current study sample comprised cases of unilateral intravitreal anti-VEGF injections ([IVI] for wet-AMD) formerly given to the patients. Inclusion criteria were a minimum of 3 IVI treatments, with at least 1 IVI treatment within the previous 3 months. The study included a control group of individuals aged 55 years and older who were in good health. Exclusion criteria were patients with bilateral wet AMD who had received IVI anti-VEGF injections, the presence of systemic diseases such as diabetes and hypertension, contact lenses, prolonged use of topical ocular medications, or a history of refractive surgery. Patients diagnosed with glaucoma and currently receiving glaucoma medication, and those who had undergone intraocular surgery other than uncomplicated phacoemulsification within the previous 6 months were also eliminated from the study.

Baseline Examination

All participants were subjected to a meticulous ophthalmic examination, which encompassed the following procedures: best-corrected visual acuity, slit-lamp examination of the anterior segment, intraocular pressure (IOP) measurement, posterior segment examination, and optical coherence tomography (OCT). OCT scanning of the macula was carried out using the Spectralis OCT instrument (software version 6.3.3.0, Heidelberg Engineering, Heidelberg, Germany).

Moreover, a high-speed OCT protocol with $15^\circ \times 20^\circ$ raster scans was used to measure macular thickness.

Intravitreal Anti-VEGF Treatment Protocol

According to Turkish health regulations, patients starting IVI anti-VEGF treatment typically receive an initial therapy of three courses of bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA). The loading dose of bevacizumab was 1.25 mg/0.05 mL, administered in three consecutive doses with an interval of 4 weeks. The decision to continue bevacizumab was based on positive clinical outcomes in response to treatment. In cases where there was no favorable response to bevacizumab, the treating physician had the discretion to switch to ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA, USA) or aflibercept (Eylea; Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) as alternative anti-VEGF agents. The choice of a specific anti-VEGF agent (ranibizumab or aflibercept) was determined by the treating physician. Ranibizumab was applied at a concentration of 0.5 mg, while aflibercept was applied at a concentration of 2.0 mg intravitreally. The frequency and duration of treatment were adjusted according to the individual patient's disease activity and response to treatment.

Injection Procedure

Topical anesthetics were used to ensure patient comfort. A sterile technique was used throughout the procedure to minimize the risk of infection. The periocular area and ocular surface were sterilized, and the eye was stabilized using a speculum or gentle eyelid traction. The anti-VEGF agent was delivered into the posterior vitreous compartment through a 30-gauge needle, typically targeting the infero-temporal or supero-temporal quadrant of the eye. A sterile cotton tip was used to apply gentle compression to the injection area to prevent the potential for bleeding and vitreous reflux. Moxifloxacin eyedrops were ordered with a step-down regimen over 7 days. The drops were applied every 4 h.

Evaluation of Tear Film and Corneal Sensitivity Measurement

The first tear film break-up time (F-BUT) and the average tear film break-up time (A-BUT) were determined through the use of a Scheimpflug tomographer and topographer (CSO, Italy).^[9] This device non-invasively analyses the tear film in selected areas of the cornea. F-BUT shows the time required for the initial tear break-up, whereas A-BUT depicts the mean break-up times of the tear film in various regions of the cornea over the time span of the imaging procedure (Fig. 1).

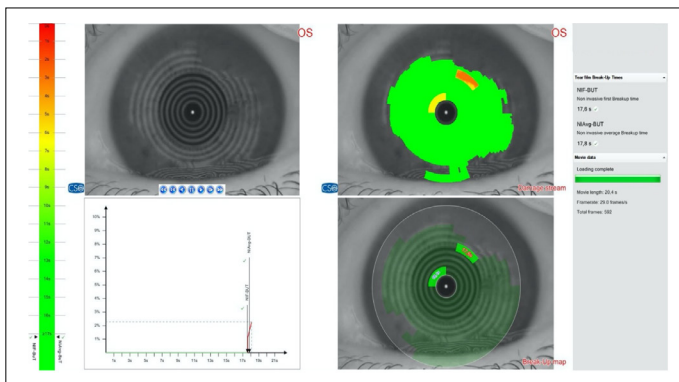


Fig. 1. Non-invasive tear break-up times (BUT) in corneal topography.

The sensitivity of the central cornea was assessed with a hand-held Cochet-Bonnet esthesiometer fitted with a 60 mm retractable nylon monofilament that can be used for varying pressure by adjusting its length (Luneau Ophthalmologie, France).^[10] The sensitivity of the corneal threshold was determined as the amount of nylon thread at which subjects responded to approximately 1/2 of the total number of stimulus presentations. This length was established by gradually retracting the filament by 5 mm until a threshold was reached. To facilitate statistical analysis, the fiber length of the Cochet-Bonnet esthesiometer was transformed into a pressure-based measurement (in g/mm^2) in accordance with the convert table from the manufacturer. As an additional assessment measure, each participant was evaluated with an ocular surface disease index (OSDI) score.^[11]

Assessment of Corneal Nerve Morphology Using in vivo Confocal Microscopy (IVCM)

All participants underwent Heidelberg Retina Tomography II confocal laser scanning IVCM (HRT III; Heidelberg Engineering, Heidelberg, Germany) equipped with a Rostock Cornea Module lens system.^[12] The microscope was focused on the corneal subbasal nerve plexus (SBNP) to obtain clear and detailed images. Each image represented an area of $400 \times 400 \mu\text{m}$ with a lateral resolution of $2 \mu\text{m}$ and an optical section thickness of $4 \mu\text{m}$ (Figs. 2 and 3).

The ACC metrics software (University of Manchester, United Kingdom) was used for image processing of nerve fibers within the SBNP.^[13] The software operates through a multi-step image processing pipeline involving preprocessing (contrast enhancement and noise reduction), edge detection, skeletonization, and segmentation of nerve fibers. Key morphological parameters were computed directly from the processed images, including: corneal nerve fiber density (CNFD; total number of major nerves per square

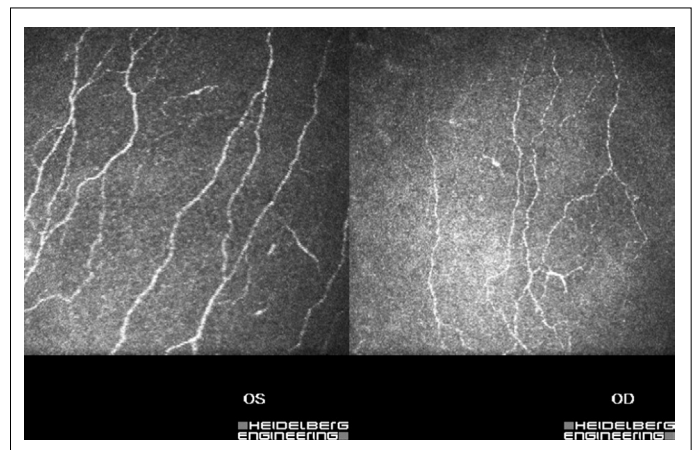


Fig. 2. In vivo confocal microscopy images of the subbasal corneal nerve plexus from the same patient. The left image shows the untreated eye, demonstrating a relatively preserved nerve fiber structure. The right image illustrates the anti-VEGF-treated eye, displaying an evident mildly reduction in subbasal nerve plexus density.

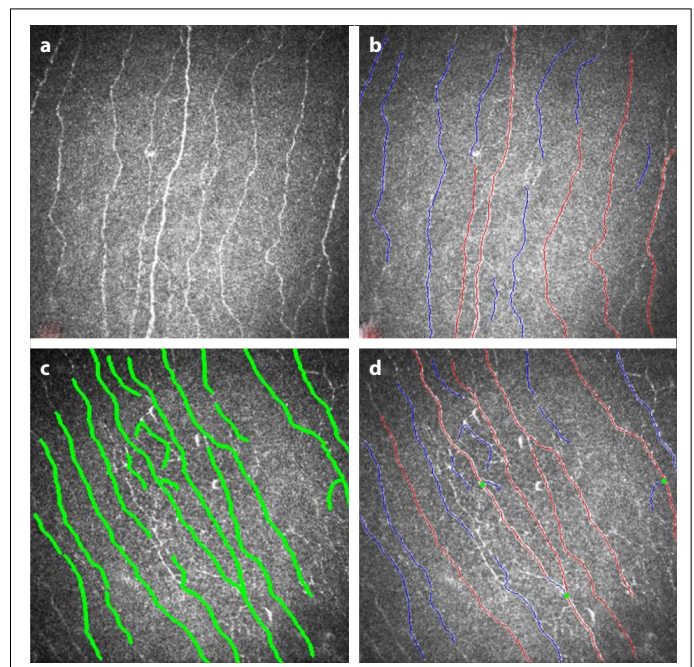


Fig. 3. Automated nerve fiber analysis using ACCMetrics software. Raw image (a) presents the original, unprocessed confocal image of the sub-basal nerve plexus. In the nerve detection image (c), an enhanced segmentation view shows the extracted nerve paths in green, visualizing the full nerve fiber structure. In the analyzed image (b and d), detected nerve fibers are classified into main axons (red), branches (blue), and branching points (green dots).

millimeter), corneal nerve branch density (CNBD; number of branches originating from major nerve trunks per square millimeter), total length of all nerve fibers and branches (CNFL; in millimeters per square millimeter), total corneal branch density (CTBD; the total number of branch points

per square millimeter), corneal nerve fiber area (CNFA; total nerve fiber area per square millimeter), corneal nerve fiber width (CNFW; mean nerve fiber width per square millimeter) and corneal nerve fiber fractal dimension (CNFracDim). The choice of a fully automated method was made to ensure high reproducibility, reduce subjective bias, and facilitate efficient processing of multiple images. For each eye, three exemplary images of superior quality were selected based on optimal image resolution, clear visualization of the relevant anatomical structures, and absence of artifacts. The selection was performed by two experienced observers (HS and EG) to ensure consistency.

To reduce interindividual variability, each patient served as their own internal control. The corneal nerve parameters of the anti-VEGF-treated eyes were directly compared with those of the untreated fellow eye. In addition, a healthy control group was included to provide normative reference values.

Statistical Analysis

The data were examined through the implementation of a statistical analysis, which was executed with the utilization of Statistical Package for Social Sciences version 22 (IBM, Chicago, USA). To determine the normality of the distribution and the homogeneity of variance within the dataset, the Shapiro–Wilk test and Levene’s test were employed. Pearson chi-square test was performed for nominal data. In the case of data that is normally distributed, expressed as mean (standard deviation), an independent and dependent samples t-test was performed. In the case of data that were not distributed normally, an analysis was conducted (with the Mann–Whitney U test and the Wilcoxon test). The resulting data were then presented as a range, including both the median and the interquartile range, with the 25th and 75th percentiles also indicated. Subgroup analyses were conducted using both analysis of variance and the Kruskal–Wallis test. A linear mixed-effects model was utilized to facilitate a cross-sectional comparison of continuous parameters. Spearman’s correlation analysis was implemented to identify the correlations between the SBNP values and other clinical parameters. In this study, a critical value of $p < 0.05$ was established as the benchmark for statistical significance.

Results

Overall, 48 patients (25 males and 23 females) and 25 healthy controls (14 males and 11 females) were enrolled. The mean age was similar between the groups ($p = 0.07$). In addition, the OSDI score for the patient group was 26.1 (11.3–49.2) compared to the control group’s OSDI score of

Table 1. Demographics and clinical features

Variables	AMD group	Control group	p
Gender (M/F)	25/23	14/11	0.750
Age (years)	68.2±7.4	64.5±9.4	0.07
IVI anti-VEGF count	13.9±8.9	-	-
OSDI (score)	26.1 (11.3–49.2)	16.6 (8.7–18.7)	0.006*

AMD: Age-related macular degeneration; IVI: Intravitreal; OSDI: Ocular surface disease index; VEGF: Vascular endothelial growth factor; *Statistical significance.

16.6 (8.7–18.7) ($p = 0.006$). The mean number of anti-VEGF injections administered was 13.9±8.9 (Table 1).

Evaluation of IVCM parameters showed a statistically significant reduction in CNFW in anti-VEGF-treated eyes compared to untreated eyes ($p = 0.002$). Other IVCM parameters, including CNFD, CNBD, CNFL, CTBD, CNFA, and CNFracDim, did not differ between treated eyes and untreated eyes (Table 2). The OSDI scores and BUT exhibited no statistically significant differences, and the corneal sensitivity was not notably different between the groups (Table 2). In subgroup analyses where treated eyes were classified according to the type of anti-VEGF injections administered, no significant difference was observed in any of the IVCM parameters or other clinical parameters (Table 3).

Age was included as a covariate. The covariate age, which appears in the model, is valued at 66.2. There was a statistically significant reduction in CNFW in anti-VEGF-treated eyes compared to healthy control eyes ($p = 0.022$), but the other parameters were not significantly different (Table 2). There was no significant difference in OSDI scores, BUT, and corneal sensitivity (Table 2).

Correlation analyses were conducted to investigate the interrelationship between IVCM parameters and other clinical variables in eyes that had undergone treatment. However, no statistically meaningful correlation was identified between these clinical parameters and the IVCM parameters (Table 4).

Discussion

The most important finding of the study was that CNFW was significantly reduced in treated eyes. This finding suggests that anti-VEGF treatment exerts a pronounced impact on the structural attributes of corneal nerves. However, other IVCM parameters did not show any significant change. In addition, there were no significant differences in BUT and corneal sensitivity. This showed that the reduction in

Table 2. AMD and control group comparison of clinical and IVCM parameters

Variables	Injected eye (n=48)	Fellow eye (n=48)	Control eye (n=25)	p ¹	p ²	p ³
F-BUT (seconds)	7.6 (2.3–21.0)	8.7 (3.0–21.0)	21.0 (2.4–21.0)	0.210	0.517	0.371
A-BUT (seconds)	12.1 (8.0–21.0)	12.7 (8.6–21.0)	21.0 (9.6–21.0)	0.185	0.421	0.381
Corneal sensitivity (g/mm ²)	0.96 (0.96–1.08)	0.96 (0.96–1.05)	0.96 (0.96–0.96)	0.101	0.294	0.399
CNFD (n/mm ²)	21.8±8.1	21.8±8.5	25.0±5.1	0.262	0.230	1.000
CNBD (n/mm ²)	27.9±17.7	33.4±22.2	34.2±25.3	0.648	0.333	0.065
CNFL (µm/mm ²)	13.6±4.1	14.0±4.2	16.2±3.2	0.298	0.417	0.514
CTBD (n/mm ²)	46.6±25.1	51.9±31.4	51.9±30	0.883	0.740	0.200
CNFA (µm ² /mm ²)	0.006±0.002	0.006±0.002	0.006±0.002	0.872	0.997	0.536
CNFW (µm/mm ²)	0.0200±0.001	0.0205±0.001	0.021±0.001	0.022*	0.456	0.002*
CNFracDim	1.44±0.04	1.47±0.04	1.49±0.02	0.110	0.200	0.351

A-BUT: Average tear film break-up time; CNFD: Corneal nerve fiber density; CNBD: Corneal nerve branch density; CNFA: Corneal nerve fiber area; CNFL: Nerve fibers and branches length; CNFracDim: Corneal nerve fiber fractal dimension; CNFW: Corneal nerve fiber width; CTBD: Total corneal branch density; F-BUT: First tear film break-up time; p¹: Injected eye versus control eye; p²: fellow eye versus control eye; p³: Injected eye versus fellow eye; *Statistical significance.

Table 3. Comparison of clinical parameters and IVCM parameters in anti-VEGF injected eye in subgroups

Variables	Bevacizumab (n=6)	Bevacizumab and Aflibercept (n=21)	Bevacizumab and Ranibizumab (n=21)	p
OSDI	34.5 (11.5–60.6)	20.4 (9.4–34.4)	30.5 (11.3–48.5)	0.536
F-BUT (second)	6.1 (1.4–12.4)	11.7 (2.7–21)	6.4 (1.9–16.7)	0.329
A-BUT (second)	11.8 (8.2–15.6)	13.5 (7.1–21)	11.5 (7.4–19.4)	0.634
Corneal sensitivity (g/mm ²)	1.06 (0.96–1.16)	0.96 (0.96–1.08)	0.96 (0.96–1.08)	0.313
CNFD (n/mm ²)	21.5±9.0	19.5±6.9	24.3±8.6	0.164
CNBD (n/mm ²)	24.9 (6.7–40.6)	27.0 (7.2–33.3)	29.1 (17.7–41.6)	0.464
CNFL (µm/mm ²)	16.1 (5.8–17.4)	13.4 (8.6–16.4)	14.7 (11.6–18)	0.454
CTBD (n/mm ²)	41.3±25.4	43.5±25.0	51.3±25.6	0.523
CNFA (µm ² /mm ²)	0.006 (0.003–0.006)	0.005 (0.004–0.007)	0.005 (0.004–0.008)	0.582
CNFW (µm/mm ²)	0.020 (0.018–0.022)	0.019 (0.018–0.020)	0.020 (0.019–0.021)	0.099
CNFracDim	1.4 (1.3–1.5)	1.4 (1.4–1.4)	1.4 (1.4–1.5)	0.173

A-BUT: Average tear film break-up time; CNFD: Corneal nerve fiber density; CNBD: Corneal nerve branch density; CNFA: Corneal nerve fiber area; CNFL: Nerve fibers and branches length; CNFracDim: Corneal nerve fiber fractal dimension; CNFW: Corneal nerve fiber width; CTBD: Total corneal branch density; F-BUT: First tear film break-up time; OSDI: Ocular surface disease index; *Statistical significance.

CNFW did not result in significant ocular surface disease or decreased corneal sensitivity. The lack of significant differences in the subgroup analyses by type of anti-VEGF injections used suggests that the different agents do not differ significantly in their effects on corneal nerves.

The OSDI score is a measure used to assess the severity and symptoms of ocular surface disease. It provides information on tear production, dry eye symptoms, and overall ocular surface health. As AMD patients tend to have dry eye symptoms, it would be expected that the OSDI score would be higher in older people than in healthy controls.^[14]

Our findings align closely with those reported by Polat et al.,^[6] who showed corneal nerve loss after repeated IVI anti-VEGF injections in AMD and diabetic macular edema

subgroups compared to healthy controls. However, the previous study included a limited number of AMD patients (20 patients) as a subgroup, and the mean ages of both the AMD patients and healthy control groups were younger than those in the current study. In addition, the authors did not report a subgroup analysis of different anti-VEGF agents because of the high drug switch ratio in their study.^[6] Moreover, Goldhardt et al.^[15] reported significant corneal nerve damage associated with serial intravitreal anti-VEGF injections. Despite some methodological differences, such as the inclusion of diabetic patients, our findings corroborate their results, further underscoring the potential adverse impact of anti-VEGF agents on corneal nerve morphology.

Table 4. Correlation analysis of IVCM parameters and clinical parameters

Variables	Anti-VEGF injection count	OSDI	F-BUT	A-BUT	Corneal sensitivity
CNFD					
r	-0.142	0.211	0.133	0.155	0.130
P	0.335	0.149	0.368	0.290	0.377
CNBD					
r	0.016	0.237	0.036	0.051	0.115
P	0.910	0.104	0.805	0.728	0.434
CNFL					
r	-0.108	0.322	0.101	0.166	0.110
P	0.463	0.025	0.493	0.257	0.453
CTBD					
r	0.059	0.190	-0.011	0.008	0.010
P	0.687	0.194	0.937	0.956	0.946
CNFA					
r	-0.074	0.184	0.004	0.056	0.064
P	0.617	0.208	0.979	0.702	0.662
CNFW					
r	-0.217	-0.108	-0.029	-0.007	0.004
P	0.138	0.463	0.843	0.960	0.974
CNFracDim					
r	-0.070	0.279	0.066	0.152	0.042
P	0.635	0.055	0.652	0.300	0.776

A-BUT: Average tear film break-up time; CNFD: Corneal nerve fiber density; CNBD: Corneal nerve branch density; CNFA: Corneal nerve fiber area; CNFL: Nerve fibers and branches length; CNFracDim: Corneal nerve fiber fractal dimension; CNFW: Corneal nerve fiber width; CTBD: Total corneal branch density; F-BUT: First tear film break-up time; OSDI: Ocular surface disease index.

Bitirgen et al.^[16] found no difference in corneal sensitivity or subbasal nerve fiber characteristics between patients receiving numerous IVI ranibizumab injections for AMD and the control group. A possible reason for this discrepancy could be related to differences in study populations, injection frequency, or methodological variations in nerve fiber analysis. Moreover, patients were compared with healthy controls in these studies.

The methods used to analyze corneal nerve function can be classified as direct or indirect measurements. Direct measures typically analyze corneal sensitivity.^[17] This provides a more direct and objective assessment of corneal nerve activity. On the other hand, indirect measures are based on the patient's symptoms and can often be more subjective. Tear testing and patients' ocular surface symptoms can provide information on corneal nerve function.^[18] Several studies have been conducted on the potential effects of anti-VEGF injections on the ocular surface, and many studies have suggested that this type of treatment may lead to various ocular surface disorders. Polat et al.^[8] compared AMD patients with healthy controls and showed that meibomian gland dysfunction increased after repeated IVI with povidone iodine and antibiotics.

However, Malmin et al.^[19] compared treated and untreated eyes in patients with unilateral AMD and found that meibomian gland dysfunction decreased in treated eyes after IVI. This interesting result in that study was attributed to the reduction of VEGF, an inflammatory cytokine, in nearby tissues as a result of IVI and the antibacterial effect of povidone iodine.^[19]

The trigeminal ganglia contain VEGF and VEGF receptors, and inhibiting VEGF signaling inhibits nerve growth and development.^[20,21] However, topical bevacizumab has not been shown to affect CNFD in one animal study,^[21] but corneal innervation was impaired by subconjunctival bevacizumab injection in another study,^[22] suggesting that the impact of anti-VEGF on corneal nerves may be contingent on the route of administration. Most IVI biologics are eliminated through the anterior chamber.^[23] IVI administration has produced conflicting results in human studies. These conflicting results suggest that more research is needed to define the pathways and mechanisms by which VEGF signaling affects corneal nerve growth and to determine its potential clinical implications. There may be compensatory mechanisms for anti-VEGF effects. The elimination of molecules from the eye may vary depending

on their chemical composition, with some molecules being cleared more rapidly than others. In addition, the extent of dispersion of these molecules within ocular tissues may differ, and they may also exhibit varying degrees of off-target effects.

Limitations of the Study

The current study has the following limitations: The first of which is the relatively limited amount of participants. Second, the use of more than one anti-VEGF agent may confound the assessment of their effects on corneal nerves. Future studies with larger, agent-specific cohorts are necessary to conclusively compare the effects of individual anti-VEGF therapies on corneal nerves. Finally, the use of IVCM, although a highly sensitive and powerful tool for imaging the cornea at the cellular level, has its own limitations in terms of reproducibility and operator dependence. Longitudinal investigations are required to confirm these results and monitor the potential long-term effects of anti-VEGF treatment on corneal nerve morphology.

Conclusion

Our investigation discovered that anti-VEGF medication resulted in a considerable reduction in CNFW. This suggests that anti-VEGF treatment may affect corneal nerve structure but does not necessarily lead to changes in corneal function.

Ethics Committee Approval: The Erciyes University Ethics Committee granted approval for this study (date: 04.10.2023, number: 2023/648).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: E.G., K.E.; Design: K.E.; Supervision: M.U.; Resource: E.G.; Materials: M.Z.; Data Collection and/or Processing: E.G., F.O.; Analysis and/or Interpretation: H.S., O.A.P., F.O., M.Z.; Literature Search: E.G.; Writing: E.G., K.E.; Critical Reviews: K.E., M.U.

Conflict of Interest: None declared

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declared that this study has received no financial support.

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