e-ISSN: 2722-9807
Sriwijaya Journal of Ophthalmology
[SJO]
https://sriwijayaophthalmology.com

Sustained Anti-VEGF Delivery via Hydrogel Implant Achieves Non-Inferior Visual and Anatomical Outcomes in Neovascular AMD: A 24-Month Randomized Controlled Trial

Habiburrahman Said[1*], Oliva Azalia Putri[2], Linda Purnama[3]

[1]Department of Health Sciences, Phlox Institute, Palembang, Indonesia
[2]Department of Surgery, CMHC Research Center, Palembang, Indonesia
[3]Department of Ophthalmology, Phlox Institute, Palembang, Indonesia

ARTICLE INFO

Keywords:
Anti-VEGF therapy
Hydrogel implant
Intravitreal injection
Neovascular age-related macular degeneration
Sustained-release drug delivery

***Corresponding author:**
Habiburrahman Said

E-mail address:
habiburrahman.said@phlox.or.id

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/sjo.v8i2.138

A B S T R A C T

Introduction: Neovascular age-related macular degeneration (nAMD) requires frequent anti-VEGF intravitreal injections, creating substantial treatment burden. This study compared the 24-month efficacy and safety of a sustained-release anti-VEGF hydrogel implant versus monthly ranibizumab in treatment-naive nAMD eyes.

Methods: This prospective randomized controlled trial enrolled 126 eyes (96 patients; 30 bilateral) with treatment-naive nAMD at a private hospital in Palembang, Indonesia (January 2022–December 2024). Eyes were randomized 1:1 to a biodegradable anti-VEGF hydrogel implant (n=64) or monthly ranibizumab 0.5 mg (n=62). The primary outcome was non-inferiority of the mean best-corrected visual acuity (BCVA) change (LogMAR) at 24 months (margin: 0.10 LogMAR). Analyses used linear mixed-effects models with generalized estimating equations to account for inter-eye correlation.

Results: Mean BCVA improved by −0.24±0.18 LogMAR (≈12 letters) in the hydrogel group and −0.22±0.20 LogMAR (≈11 letters) in the ranibizumab group (difference: −0.02; 95% CI: −0.09 to 0.05; p=0.578; non-inferiority confirmed). The hydrogel group required 77.8% fewer injections (4.8±1.2 vs 21.6±3.4; p<0.001). Safety profiles were comparable.

Conclusion: The sustained-release anti-VEGF hydrogel implant achieved non-inferior visual and anatomical outcomes versus monthly ranibizumab while reducing injection burden by 77.8% over 24 months. Multicenter validation is warranted.

1. Introduction

Age-related macular degeneration (AMD) remains the leading cause of irreversible central vision loss among adults aged 50 years and older worldwide. Approximately 196 million people were affected globally in 2020, a figure projected to rise to 288 million by 2040, and the most recent Global Burden of Disease Study 2021 confirms a continuing rise in AMD-related vision impairment through 2050.[1,2] The neovascular form (nAMD), characterized by choroidal neovascularization (CNV) driven by dysregulated vascular endothelial growth factor (VEGF) signaling, accounts for approximately 10–15% of all AMD cases but is responsible for nearly 90% of severe vision loss.[3] In Southeast Asian

populations, including Indonesia, the prevalence of nAMD is increasing rapidly, with polypoidal choroidal vasculopathy (PCV) representing a particularly common subtype that may influence treatment response.[4,5]

Intravitreal anti-VEGF therapy fundamentally transformed nAMD management, with ranibizumab and aflibercept established as standard of care.[6,7] The therapeutic armamentarium has since expanded toward longer-acting agents: faricimab, a bispecific angiopoietin-2/VEGF-A inhibitor, achieved non-inferior visual outcomes with dosing intervals extended up to 16 weeks in the phase 3 TENAYA and LUCERNE trials,[8,9] and high-dose aflibercept 8 mg achieved 12–16-week dosing intervals in the PULSAR trial.[10] Network meta-analyses confirm that these newer agents reduce injection frequency while preserving efficacy.[11] Despite these advances, real-world studies consistently demonstrate that undertreatment—driven by appointment non-adherence, patient burden, and healthcare-system constraints—remains the primary driver of suboptimal visual outcomes.[12,13]

Treatment burden imposes substantial demands on patients, caregivers, and health systems, with monitoring visits and frequent injections consuming considerable time and resources.[14] Patient-reported outcome studies confirm that injection-related anxiety, clinic-visit frequency, and cumulative costs represent significant barriers to adherence.[15] Sustained-release drug delivery systems represent a paradigm shift in this context. The Port Delivery System with ranibizumab demonstrated efficacy with 24-week refills but requires surgical implantation,[16,17] and a range of long-acting delivery platforms are now under active development.[18]

Biodegradable hydrogel-based implants offer minimally invasive, injectable delivery with sustained intravitreal drug release.[19,20] Preclinical studies have demonstrated favorable pharmacokinetic profiles over three to six months; however, no published randomized controlled trial has evaluated long-term efficacy beyond 12 months. The aim of this study was to evaluate the 24-month efficacy and safety of a biodegradable sustained-release anti-VEGF hydrogel implant compared with standard monthly intravitreal ranibizumab in treatment-naive nAMD eyes, using a non-inferiority design with a margin of 0.10 LogMAR.[21]

2. Methods

Study design and setting

This prospective, single-center, open-label, parallel-group, randomized controlled non-inferiority trial was conducted at the ophthalmology clinic of a private hospital in Palembang, Indonesia (January 2022–December 2024). The study was approved by the CMHC Ethics Committee (Approval No. CMHC/EC/2022/0147), and written informed consent was obtained from all participants. The trial was registered at ClinicalTrials.gov (NCT05482671). BCVA measurements were performed by a masked certified optometrist independent of the treating ophthalmologist.

Participants

Eligible patients were treatment-naive, aged ≥50 years, with active subfoveal or juxtafoveal CNV secondary to nAMD confirmed by spectral-domain optical coherence tomography (SD-OCT) and fluorescein angiography (FA). Inclusion criteria were BCVA of 0.30–1.00 LogMAR, central retinal thickness (CRT) >300 μm, and active CNV (subretinal, intraretinal, or sub-RPE fluid). Exclusion criteria were prior anti-VEGF, photodynamic therapy or laser, prior vitreoretinal surgery, active ocular infection, intraocular pressure (IOP) >25 mmHg, diabetic retinopathy, and HbA_{1c} >9.0%.

Sample Size

With a non-inferiority margin of 0.10 LogMAR (≈5 ETDRS letters), an assumed SD of 0.20 LogMAR, a one-sided α=0.025, and power of 0.80, a minimum of 52 eyes per group was required. Allowing for 20% dropout, 126 eyes were enrolled.

Randomization and intervention

Computer-generated 1:1 block randomization (blocks of 4 and 6) was stratified by baseline BCVA (≤0.50 vs >0.50 LogMAR) and CNV type. Allocation concealment was maintained via a centralized REDCap system. Bilateral eyes were independently randomized. The hydrogel group received a PEG-based hydrogel microsphere implant (HydroRelease-R; 0.5 mg ranibizumab loaded, delivered by 25-gauge trocar), with re-implantation per OCT reactivation criteria. The ranibizumab group received 0.5 mg monthly ×3 loading followed by monthly pro re nata (PRN) dosing per identical criteria.

Ophthalmic examinations

Visits were scheduled at baseline and months 1, 2, 3, 6, 9, 12, 18, and 24. BCVA was measured using ETDRS charts at 4 m by a masked optometrist, with manifest refraction at every visit under 85 cd/m² illumination (ICC=0.96). IOP was measured by Goldmann applanation tonometry pre-dilation at the same time of day (±2 h), and both pre- and 30-minutes post-injection. SD-OCT was performed using Heidelberg Spectralis (49 B-scans, ART ≥16, signal >20 dB, eye tracking, baseline registration). CRT was measured in the central 1 mm ETDRS subfield, excluding pigment epithelial detachment. FA was performed at baseline, month 12, and month 24.

Statistical analysis

The intention-to-treat (ITT) analysis (n=126) was complemented by a per-protocol sensitivity analysis (n=121). The primary analysis used a linear mixed-model for repeated measures with treatment, time, baseline BCVA, and stratification variables as fixed effects and patient as a random effect. Generalized estimating equations accounted for inter-eye correlation (ICC=0.72). Worst-case and unilateral-only sensitivity analyses were performed. Secondary outcomes were exploratory and unadjusted for multiplicity. Multivariate logistic regression was used for the ≥15-letter gain outcome, and Cohen's d quantified effect size. A two-sided $p<0.05$ was considered significant, except for the primary non-inferiority test (one-sided $p<0.025$).

3. Results

Of 142 screened eyes, 126 were randomized (hydrogel n=64, ranibizumab n=62). Five eyes (3.9%) were lost to follow-up (non-differential, p=1.000). Baseline demographic and ocular characteristics were well balanced between the two groups, as detailed in Table 1. Mean age was 71.3±8.2 versus 70.8±7.9 years, and baseline BCVA was 0.62±0.28 versus 0.58±0.26 LogMAR (p=0.398).

Table 1. Baseline demographic and ocular characteristics.

Parameter	Hydrogel (n=64)	Ranibizumab (n=62)	p-value
Age (years), mean ± SD	71.3 ± 8.2	70.8 ± 7.9	0.724
Female, n (%)	36 (56.3)	33 (53.2)	0.727
Diabetes mellitus, n (%)	18 (28.1)	16 (25.8)	0.776
Hypertension, n (%)	41 (64.1)	39 (62.9)	0.887
Smoking history, n (%)	22 (34.4)	20 (32.3)	0.802
BCVA LogMAR, mean ± SD	0.62 ± 0.28	0.58 ± 0.26	0.398
CRT (μm), mean ± SD	412.5 ± 98.7	405.3 ± 102.4	0.681
IOP (mmHg), mean ± SD	14.8 ± 3.1	15.1 ± 2.9	0.571
SRF present, n (%)	58 (90.6)	55 (88.7)	0.734

At 24 months (ITT), the mean BCVA change was −0.24±0.18 LogMAR in the hydrogel group versus −0.22±0.20 LogMAR in the ranibizumab group; the between-group difference was −0.02 (95% CI: −0.09 to 0.05; p=0.578; Cohen's d=0.10). The upper bound of the confidence interval (0.05) was within the pre-specified non-inferiority margin (0.10 LogMAR), confirming non-inferiority; the worst-case analysis yielded an upper CI bound of 0.08, still within the margin. CRT decreased by 148.2±78.5 versus 152.6±82.3 µm (p=0.758), and subretinal fluid (SRF) resolution was 79.7% versus 80.6%. The injection count was 4.8±1.2 versus 21.6±3.4 (p<0.001), representing a 77.8% reduction. These primary and secondary outcomes are summarized in Table 2, and the temporal trajectory of mean BCVA over the 24-month period for both groups is shown in Figure 1.

Table 2. Primary and secondary outcomes at 24 months (ITT).

Outcome	Hydrogel	Ranibizumab	Diff (95% CI)	p
ΔBCVA LogMAR†	−0.24±0.18	−0.22±0.20	−0.02 (−0.09, 0.05)	0.578
≥15-letter gain, n (%)	28 (43.8)	29 (46.8)	OR 0.89 (0.44, 1.78)	0.739
ΔCRT (µm)‡	−148.2±78.5	−152.6±82.3	4.4 (−23.8, 32.6)	0.758
SRF resolved, n (%)	51 (79.7)	50 (80.6)	OR 0.94 (0.39, 2.28)	0.895
Total injections§	4.8±1.2	21.6±3.4	−16.8 (−17.9, −15.7)	<0.001
Injection-free interval (wk)	16.4±4.8	4.3±0.4	12.1 (10.7, 13.5)	<0.001

Notes: †Primary outcome; non-inferiority confirmed. ‡Negative value = improvement. §p<0.001. Secondary outcomes are exploratory.

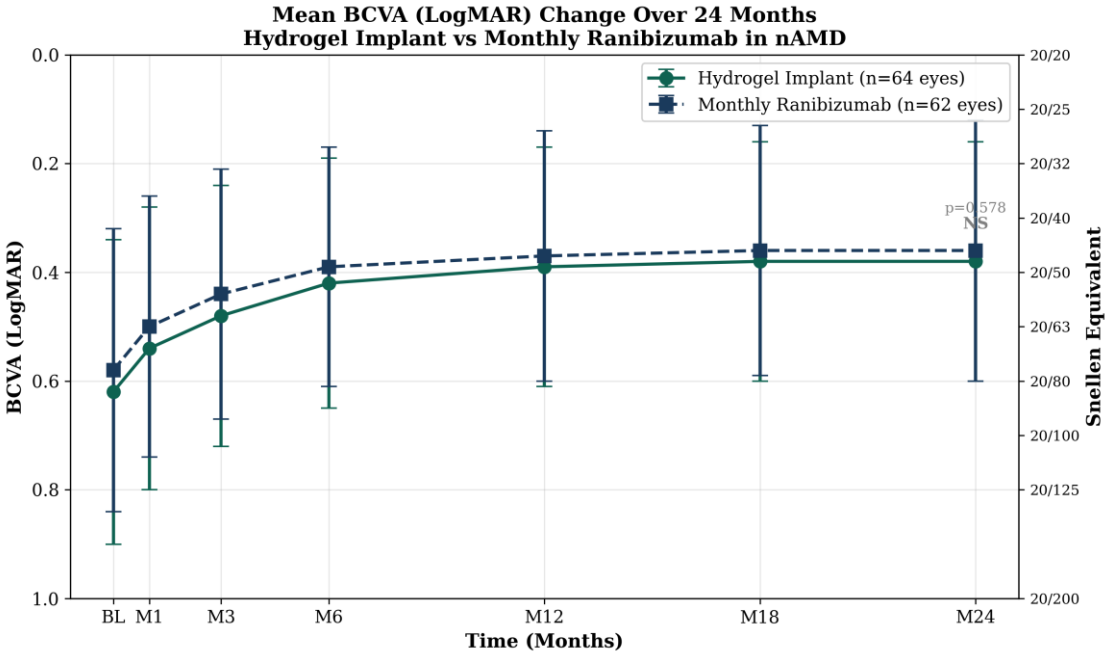

Figure 1. Mean BCVA (LogMAR) over 24 months. Error bars denote SD. Non-inferiority was confirmed at month 24.

Multivariate logistic regression identified baseline BCVA as the only independent predictor of a ≥15-letter gain (adjusted OR 1.34; 95% CI: 1.08–1.66; p=0.008), whereas treatment group was not associated with the outcome (adjusted OR 0.92; 95% CI: 0.45–1.88; p=0.826). These multivariate results are illustrated in the forest plot in Figure 2.

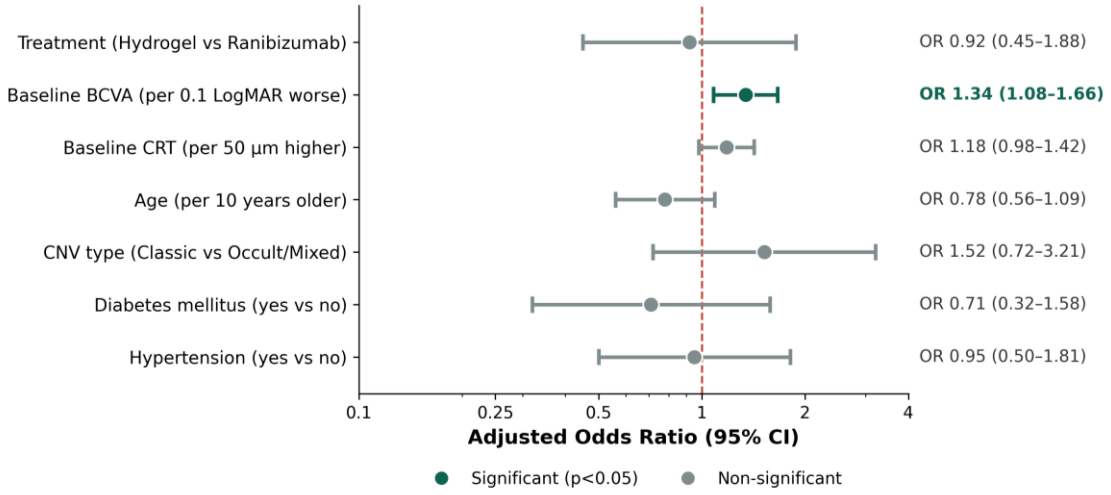

Figure 2. Forest plot of the multivariate analysis for ≥15-letter BCVA gain. Teal denotes a statistically significant association (p<0.05).

Safety was comparable between groups. Endophthalmitis occurred in 1 eye (1.6%) per group, and sustained IOP elevation in 3 eyes (4.7%) versus 2 eyes (3.2%). Subconjunctival hemorrhage was less frequent in the hydrogel group (8 eyes, 12.5%) than the ranibizumab group (18 eyes, 29.0%; p=0.021; interpret cautiously given multiplicity). The substantial difference in treatment burden between the two groups—in both total injection number and mean injection-free interval—is depicted in Figure 3.

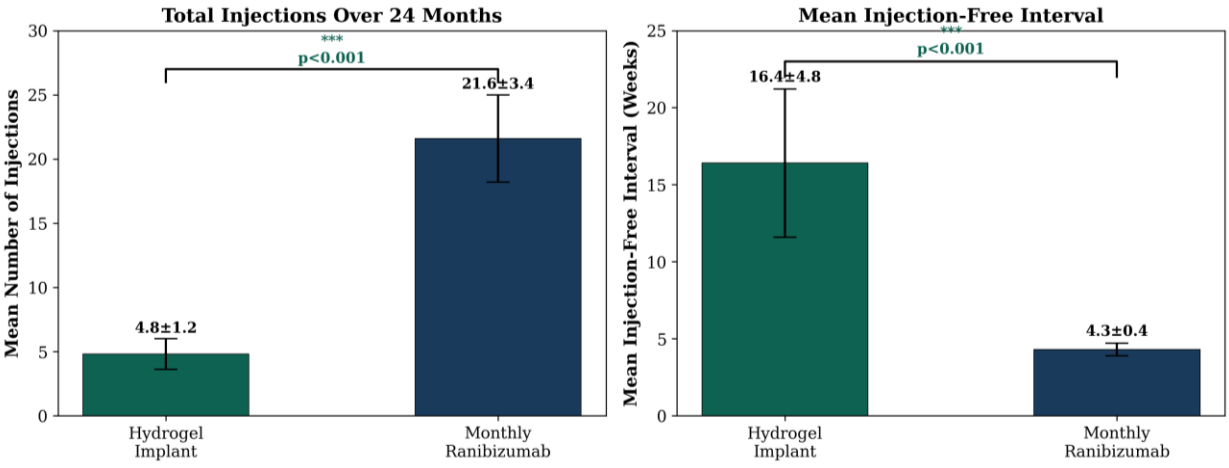

*Figure 3. Treatment burden comparison. (A) Total injections over 24 months. (B) Mean injection-free interval. ***p<0.001.*

4. Discussion

This 24-month RCT demonstrated that the sustained-release anti-VEGF hydrogel implant achieved non-inferior visual and anatomical outcomes compared with monthly ranibizumab while reducing injection burden by 77.8%. Both groups achieved a BCVA improvement of approximately 11–12 ETDRS letters, with comparable CRT reduction and fluid-resolution rates. The between-group difference of 0.02 LogMAR (Cohen's d=0.10) is clinically negligible (≈1 letter).

The 77.8% injection reduction is comparable to that of the Port Delivery System (≈75%) and exceeds the interval extensions reported for faricimab (≈40–50%) and high-dose

aflibercept.[9,10,17] The mean injection-free interval of 16.4 weeks (range 10–26; median time to re-implantation 22 weeks) is consistent with the intended 6-month release profile of the PEG-based hydrogel matrix.[19,20]

Real-world Asian cohorts typically report more modest visual gains than randomized trials, reflecting undertreatment and monitoring constraints.[22] Our larger gains reflect the treatment-naive population and protocol-mandated monitoring. The potential presence of undiagnosed PCV (≈25% mixed CNV) was balanced between groups and would not differentially bias the non-inferiority comparison.

The safety profile was favorable, with no implant-specific complications. Sustained IOP elevation is a recognized risk of repeated intravitreal anti-VEGF injections and warrants monitoring in both delivery paradigms.[23] The higher per-injection endophthalmitis rate in the hydrogel group (0.33% vs 0.075%) may reflect the larger-gauge trocar; the favorable overall biocompatibility is consistent with emerging evidence on the safety of intravitreal implants.[24] The reduced subconjunctival hemorrhage (12.5% vs 29.0%) reflects the smaller number of procedures.

Strengths of this study include its status as the first 24-month RCT of this technology, the treatment-naive population, masked BCVA assessment, and comprehensive sensitivity analyses. Limitations include the open-label design, single-center private-hospital setting, insufficient power for secondary outcomes, the absence of indocyanine green angiography for PCV identification, and ethnic homogeneity.

5. Conclusion

The sustained-release anti-VEGF hydrogel implant achieved non-inferior BCVA and anatomical outcomes versus monthly ranibizumab with 77.8% fewer injections over 24 months. Baseline BCVA was the strongest predictor of visual gain. Multicenter trials with larger samples, masked allocation, cost-effectiveness analysis, and PCV subtyping are warranted.

Ethical Approval. This study was approved by the CMHC Ethics Committee (Approval No. CMHC/EC/2022/0147). Written informed consent was obtained from all participants.

Conflict of Interest. The authors declare no conflicts of interest.

6. References

1. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014; 2(2): e106–16.
2. GBD 2021 Blindness and Vision Impairment Collaborators. Global burden of vision impairment due to age-related macular degeneration, 1990–2021, with forecasts to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Glob Health. 2025; 13(7): e1175–90.
3. Thomas CJ, Mirza RG, Gill MK. Age-related macular degeneration. Med Clin North Am. 2021; 105(3): 473–91.
4. Dat DT, Hien NDTN, Quan NN, et al. Current trends in clinical characteristics, diagnosis, and treatment of polypoidal choroidal vasculopathy: a perspective from Vietnam. J Clin Med. 2022; 11(16): 4678.
5. Zeng Y, Qiu B, Chen X, et al. OCT and OCTA quantitative metrics for polypoidal choroidal vasculopathy. BMJ Open Ophthalmol. 2025; 10(1): e002132.
6. Iida T, Gomi F, Yasukawa T, et al. Japanese clinical guidelines for neovascular age-related macular degeneration. Jpn J Ophthalmol. 2025; 69(4): 639–60.

7. Śpiewak D, Drzyzga Ł, Dorecka M, et al. Summary of the therapeutic options for patients with dry and neovascular AMD. J Clin Med. 2024; 13(14): 4227.
8. Heier JS, Khanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. Lancet. 2022; 399(10326): 729–40.
9. Khanani AM, Kotecha A, Chang A, et al. TENAYA and LUCERNE: two-year results from the phase 3 neovascular age-related macular degeneration trials of faricimab with treat-and-extend dosing in year 2. Ophthalmology. 2024; 131(8): 914–26.
10. Lanzetta P, Korobelnik JF, Heier JS, et al. Intravitreal aflibercept 8 mg in neovascular age-related macular degeneration (PULSAR): 48-week results from a randomised, double-masked, non-inferiority, phase 3 trial. Lancet. 2024; 403(10432): 1141–52.
11. Wojciechowski P, Wdowiak M, Panek M, et al. Efficacy, safety, and injection frequency with novel aflibercept 8 mg in neovascular age-related macular degeneration: a comparison with existing anti-VEGF regimens using a Bayesian network meta-analysis. Ophthalmol Ther. 2025; 14(4): 733–53.
12. Parravano M, Viola F, Nicolò M, et al. Real-world evidence of anti-VEGF therapies in patients with neovascular age-related macular degeneration in Italy: the RADIANCE study. Eur J Ophthalmol. 2025; 35(4): 1366–75.
13. Liu S, Liu Y, Wu X, et al. Efficacy and prognostic factors of anti-VEGF treatment for neovascular age-related macular degeneration: an OCTA imaging-based deep learning analysis. Photodiagnosis Photodyn Ther. 2025; 55: 104701.
14. Pina Marín B, Gajate Paniagua NM, Gómez-Baldó L, et al. Burden of disease assessment in patients with neovascular age-related macular degeneration in Spain: results of the AMD-MANAGE study. Eur J Ophthalmol. 2021; 32(1): 385–94.
15. Vinge E, Bro T. Treatment burden on patients receiving intravitreal anti-VEGF for wet age-related macular degeneration. Acta Ophthalmol. 2023; 102(4): 478–82.
16. Chandrasekaran PR, Madanagopalan VG. Ranibizumab port delivery system in neovascular age-related macular degeneration. Ther Adv Ophthalmol. 2022; 14: 25158414211072623.
17. Jaffe GJ, Cameron B, Barteselli G, et al. Macular atrophy-related observations in eyes treated with the Port Delivery System with ranibizumab in the Archway trial. Ophthalmol Retina. 2025; 9(8): 767–73.
18. Rowe LW, Ciulla TA. Long-acting delivery and therapies for neovascular age-related macular degeneration. Expert Opin Biol Ther. 2024; 24(8): 799–814.
19. Zhang C, Wang J, Wu H, et al. Hydrogel-based therapy for age-related macular degeneration: current innovations, impediments, and future perspectives. Gels. 2024; 10(3): 158.
20. Seber E, Yaylacı S. Sustained drug delivery systems for age-related macular degeneration: advancements, challenges, and future perspectives. Adv Exp Med Biol. 2025; 1499: 71–86.
21. International Conference on Harmonisation (ICH) Expert Working Group. Choice of control group and related issues in clinical trials (ICH E10). Geneva: ICH; 2000.
22. Kelkar AS, Kelkar J, Bolisetty M, et al. Visual outcomes, safety profile and morphometric

response of optical coherence tomography biomarkers to ranibizumab biosimilar treatment in neovascular age-related macular degeneration: real-world evidence. Indian J Ophthalmol. 2021; 69(6): 1469–74.

23. Levin AM, Chaya CJ, Kahook MY, et al. Intraocular pressure elevation following intravitreal anti-VEGF injections: short- and long-term considerations. J Glaucoma. 2021; 30(12): 1019–26.

24. da Silva CN, Inoue TT, França Dias M, et al. Intravitreal implants for drug delivery: clinical efficacy, safety, and translational perspectives. Expert Opin Drug Deliv. 2026; 23(5): 841–59.