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Outcomes and predictive factors for fluid resolution following three loading injections of faricimab for treatment-naïve neovascular age-related macular degeneration

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To evaluate the outcomes and predictive factors for fluid resolution following three loading injections of faricimab for neovascular age-related macular degeneration(AMD). This retrospective study included patients diagnosed with treatment-naïve neovascular AMD who received three monthly injections of faricimab. Changes in best-corrected visual acuity(BCVA) and central retinal thickness(CRT) following treatment were evaluated. The resolution of subretinal fluid(SRF), intraretinal fluid(IRF), and serous pigment epithelial detachment(PED) was also assessed. In addition, factors associated with complete resolution of SRF and IRF were investigated. A total of 69 patients were included in this study. BCVA significantly improved from a mean logarithm of minimal angle of resolution of 0.64 ± 0.41 at baseline to 0.47 ± 0.39 at 3 months ($P < 0.001$). CRT significantly decreased from 424.1 ± 155.5 μm at baseline to 266.3 ± 71.7 μm at 3 months ($P < 0.001$). At baseline, SRF was observed in 55 eyes (79.7%), IRF in 39 eyes(56.5%), and serous PED in 57 eyes(82.6%). By 3 months, the number of eyes showing these findings had decreased to 11 eyes(15.9%) for SRF, 6 eyes(8.7%) for IRF, and 10 eyes(14.5%) for serous PED. The presence of type 2 (88.2%) and type 3 (94.7%) macular neovascularization(MNV) was associated with a high incidence of complete resolution of SRF and IRF after treatment. Three loading injections of faricimab resulted in significant functional and anatomical improvements in treatment-naïve neovascular AMD, with a high rate of resolution of SRF, IRF, and serous PED. The anatomical effects were especially pronounced in cases of type 2 and type 3 MNV.

Keywords Age-related macular degeneration, Choroidal neovascularization, Faricimab, Macular neovascularization

Anti-vascular endothelial growth factor (anti-VEGF) therapy is an effective treatment for neovascular age-related macular degeneration (AMD) that significantly contributes to the prevention of blindness in patients with this condition[1]. Ranibizumab was approved by the Food and Drug Administration in 2006; aflibercept was introduced in and widely used from 2011[2,3]; and brolucizumab was introduced in 2019[4].

Faricimab (Vabysmo®, Roche, Basel, Switzerland), a more recent anti-VEGF drug, was introduced in 2022 as the first bispecific antibody drug in the field of ophthalmology. It simultaneously inhibits both VEGF-A and angiopoietin-2 and was developed with the expectation of achieving a longer-lasting effect compared to previously commercialized anti-VEGF agents[5–7].

In the TENAYA/LUCERNE study, which compared the efficacy and safety of faricimab to aflibercept in patients with neovascular AMD, faricimab demonstrated comparable visual outcomes at 48 weeks with fewer injections[7]. These results were consistently observed in analyses conducted on Asian patients as well[8]. Furthermore, patients treated with faricimab during the initial three loading injections exhibited a greater reduction in retinal fluids[7], suggesting that faricimab may exert a faster effect than aflibercept.

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Recent real-world studies have reported the therapeutic effects of initial loading injections of faricimab[9–12]. However, studies involving treatment-naïve patients remain limited[13], and most previous studies included a relatively small sample size. In the present study, we evaluated the outcomes of faricimab loading injections in a relatively large cohort of patients with neovascular AMD, focusing specifically on the anatomical outcomes and factors associated with the complete resolution of retinal fluid following treatment.

Materials and methods

This retrospective observational study was conducted at a single center (Kim's Eye Hospital, Seoul, South Korea). The study was approved by the Institutional Review Board (IRB) of Kim's Eye Hospital and conducted in accordance with the principles outlined in the Declaration of Helsinki. The need to obtain informed consent was waived by Kim's Eye Hospital IRB.

Patients and treatment

This study included consecutive patients diagnosed with treatment-naïve neovascular AMD who received three monthly injections of faricimab (6.0 mg/0.05 ml) between September 2023 and June 2024. The exclusion criteria were as follows: (1) the absence of indocyanine-green angiography (ICGA) results at diagnosis; (2) the presence of polypoidal choroidal vasculopathy (PCV), characterized by the presence of polypoidal lesions with or without a branching vascular network on ICGA; (3) extensive macular hemorrhage that hindered accurate classification based on angiography; (4) a previous history of vitrectomy or glaucoma surgery; and (5) the development of vitreous hemorrhage during the treatment period that obstructed the assessment of retinal fluid status. Patients with prior symptoms were enrolled if both eyes met the inclusion criteria.

At diagnosis, best-corrected visual acuity (BCVA) was assessed in all patients, and fundus photography (CX-1®, Topcon, Tokyo, Japan) along with optical coherence tomography (OCT) (Spectralis®, Heidelberg Engineering, Heidelberg, Germany) were conducted. Fluorescein angiography and ICGA images were also obtained using Spectralis (HRA + OCT®, Heidelberg Engineering, Heidelberg, Germany). BCVA measurements and OCT examinations were repeated for all patients 1 month after the third injection and during the second and third injections if deemed necessary by the physician.

Outcome measures

In all patients, baseline BCVA and central retinal thickness (CRT) were compared with measurements obtained at 3 months (1 month after the third faricimab injection). The presence of subretinal fluid (SRF), intraretinal fluid (IRF), and serous pigment epithelial detachment (PED) was assessed using OCT images, and the proportion of patients exhibiting these pathological findings was determined at both baseline and 3 months.

The identification and classification of PED were performed on the basis of methods suggested by Merjen et al.[14]PEDs appear as sharply demarcated elevations of the retinal pigment epithelium, and those showing homogeneously hyporeflective internal features were diagnosed as serous PED. Cases containing a serous PED component—specifically pure serous PED or mixed serous and vascularized PED—were classified as having serous PED present. The resolution of the serous component was defined as the absence of serous PED, regardless of the presence of vascularized PED. However, while a previous study[14] used multimodal imaging to assess PED, this study utilized only OCT for the PED assessment.

The type of MNV was classified as type 1 (sub-retinal pigment epithelial), type 2 (subretinal), or type 3 (intraretinal)[15,16] based on OCT and angiography results. Mixed type 1 and type 2 MNV were categorized under the type 2 MNV group. The changes in the proportions of SRF, IRF, and serous PED before and after treatment were assessed for each MNV type. Multivariate analysis was conducted to identify factors associated with the complete resolution of SRF and IRF following three loading injections. The factors included in the analysis were age, MNV type (type 1, type 2, or type 3), CRT, SRF, IRF, and serous PED.

In cases where OCT imaging was also conducted at 1 month (after the first injection) and 2 months (after the second injection), the frequency of SRF, IRF, and serous PED was assessed at each time point (baseline, 1 month, 2 months, and 3 months). The resolution patterns of each fluid compartment were analyzed over time. All images were independently analyzed by two examiners (J.H.K. and S.M.P.). The results from the more experienced senior examiner (J.H.K.) were used, and inter-examiner agreement was assessed to evaluate the reliability of the image assessment.

Statistical analysis

Data are presented as the mean ± standard deviation or as the number (%), as appropriate. Comparisons between two time points were performed using paired t-tests. Multivariate analysis was performed using binary logistic regression. A Kaplan-Meier analysis with a log-rank test was performed to compare the complete fluid resolution among the different types of MNV. Statistical analyses were performed using SPSS for Windows, version 21.0 (IBM, Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

Results

A total of 69 eyes (from 69 patients) were included in the study (Table 1).

The mean age of the patients was 76.9 ± 8.7 years. Among the cases, 33 were classified as type 1 MNV (47.8%), 17 as type 2 MNV (24.6%), and the remaining 19 (27.5%) as type 3 MNV. The BCVA was improved from a mean logarithm of minimal angle of resolution (logMAR) of 0.64 ± 0.41 (Snellen equivalent = 20/87) at baseline to 0.47 ± 0.39 (20/59) at 3 months ($P < 0.001$; Fig. 1A).

Characteristics	Values
Age, years	76.9 ± 8.7
Sex, men: women	38 (55.1%):31 (44.9%)
Type of macular neovascularization	
Type 1	33 (47.8%)
Type 2	17 (24.6%)
Type 3	19 (27.5%)
Best-corrected visual acuity, logMAR	0.64 ± 0.41
Central retinal thickness, μm	424.1 ± 155.5
Presence of subretinal fluid	55 (79.7%)
Presence of intraretinal fluid	39 (56.5%)
Presence of serous PED	57 (82.6%)

Table 1. Baseline characteristics of the included patients ($n = 69$). Data are presented as the mean ± standard deviation or as the number (%), as appropriate. logMAR, logarithm of minimum angle of resolution; PED, pigment epithelial detachment.

A ≥ 0.2 logMAR improvement in BCVA was observed in 25 eyes (36.2%), while a ≥ 0.2 logMAR deterioration was observed in two eyes (2.9%). The CRT significantly decreased from 424.1 ± 155.5 μm at baseline to 266.3 ± 71.7 μm at 3 months ($P < 0.001$; Fig. 1B).

At baseline, SRF was present in 55 eyes (79.7%), IRF in 39 eyes (56.5%), and serous PED in 57 eyes (82.6%; Fig. 2A).

By 3 months, the number of eyes exhibiting these findings decreased to 11 eyes (15.9%) for SRF, 6 eyes (8.7%) for IRF, and 10 eyes (14.5%) for serous PED. At 3 months, complete resolution of SRF and IRF was observed in 56 eyes (81.2%), with an incidence of 69.7% (23/33 eyes) for type 1 MNV, 88.2% (15/17 eyes) for type 2 MNV, and 94.7% (18/19 eyes) for type 3 MNV. Figure 3 presents representative cases of type 2 MNV (Fig. 3A–C) and type 3 MNV (Fig. 3D–F) treated with faricimab.

Multivariate analysis revealed that the presence of type 2 MNV ($P = 0.029$, $\beta = 27.856$) and type 3 MNV ($P = 0.048$, $\beta = 17.098$) were significantly associated with the complete resolution of retinal fluid following three loading injections (Table 2).

Among the 69 eyes, mild intraocular inflammation was observed in one eye (1.4%). Grade 1 (1+) anterior chamber inflammation was diagnosed one week after the faricimab injection, with the patient reporting mild floater symptoms. No signs of retinal inflammation or vascular obstruction were detected, and vitritis was not observed. The inflammation completely resolved after one week of topical steroid therapy. A RPE tear developed in two eyes (2.9%). No severe complications, such as endophthalmitis or retinal vasculitis, were reported.

OCT results were available for 53 eyes at 1 month and 2 months (24 with type 1 MNV, 12 with type 2 MNV, and 17 with type 3 MNV). In these patients, the incidence of SRF was 77.4% at baseline, which decreased to 28.3% by 1 month, 17.0% by 2 months, and 17.0% by 3 months (Fig. 2B). The incidence of IRF was 62.3% at baseline, which decreased to 11.3% by 1 month, 9.4% by 2 months, and 7.5% by 3 months. The incidence of serous PED was 83.0% at baseline, which decreased to 30.5% by 1 month, 20.8% by 2 months, and 15.1% by 3 months, respectively. Figure 4 shows the cumulative incidence of complete resolution of SRF and IRF by treatment period, stratified by MNV types.

The intraclass correlation coefficients between the two examiners were 0.942 for evaluating the presence or absence of retinal fluids, including SRF, IRF, and serous PED. The value for classifying the type of MNV was 0.890.

Discussion

In the present study, significant improvements in visual acuity and reductions in CRT were observed following faricimab loading injections. Complete resolution of SRF and IRF occurred in approximately 80% of patients, which was evident as early as after the first injection.

Faricimab is a bispecific antibody that targets both VEGF-A and angiopoietin-2. Angiopoietin-2 competes with angiopoietin-1 for binding to the Tie-2 receptor, thereby blocking the receptor's activation by angiopoietin-1. Inhibiting angiopoietin-2 enhances Tie-2 activation, which triggers anti-inflammatory and anti-permeability effects, contributing to the stabilization of blood vessels[17,18]. Based on this mechanism of action, faricimab is expected to demonstrate excellent efficacy in mitigating exudative changes associated with neovascular AMD[18]. Todoroki et al. recently reported a significant decrease in aqueous angiopoietin-2 concentrations when switching from aflibercept to faricimab, highlighting the efficacy of faricimab in suppressing Ang-2[19].

The phase 3 clinical trials TENAYA and LUCERNE, which compared the treatment outcomes of faricimab and aflibercept, were designed to demonstrate the prolonged efficacy of faricimab[20]. A notable finding of this study is that faricimab yielded superior initial anatomical outcomes compared to aflibercept. The proportion of patients achieving complete resolution of SRF and IRF during the initial loading injections was 60% at 1 month, 72% at 2 months, and 77% at 3 months in the faricimab treatment group. In contrast, the aflibercept treatment group exhibited lower rates of resolution, at 49%, 62%, and 67% at the corresponding time points, respectively.

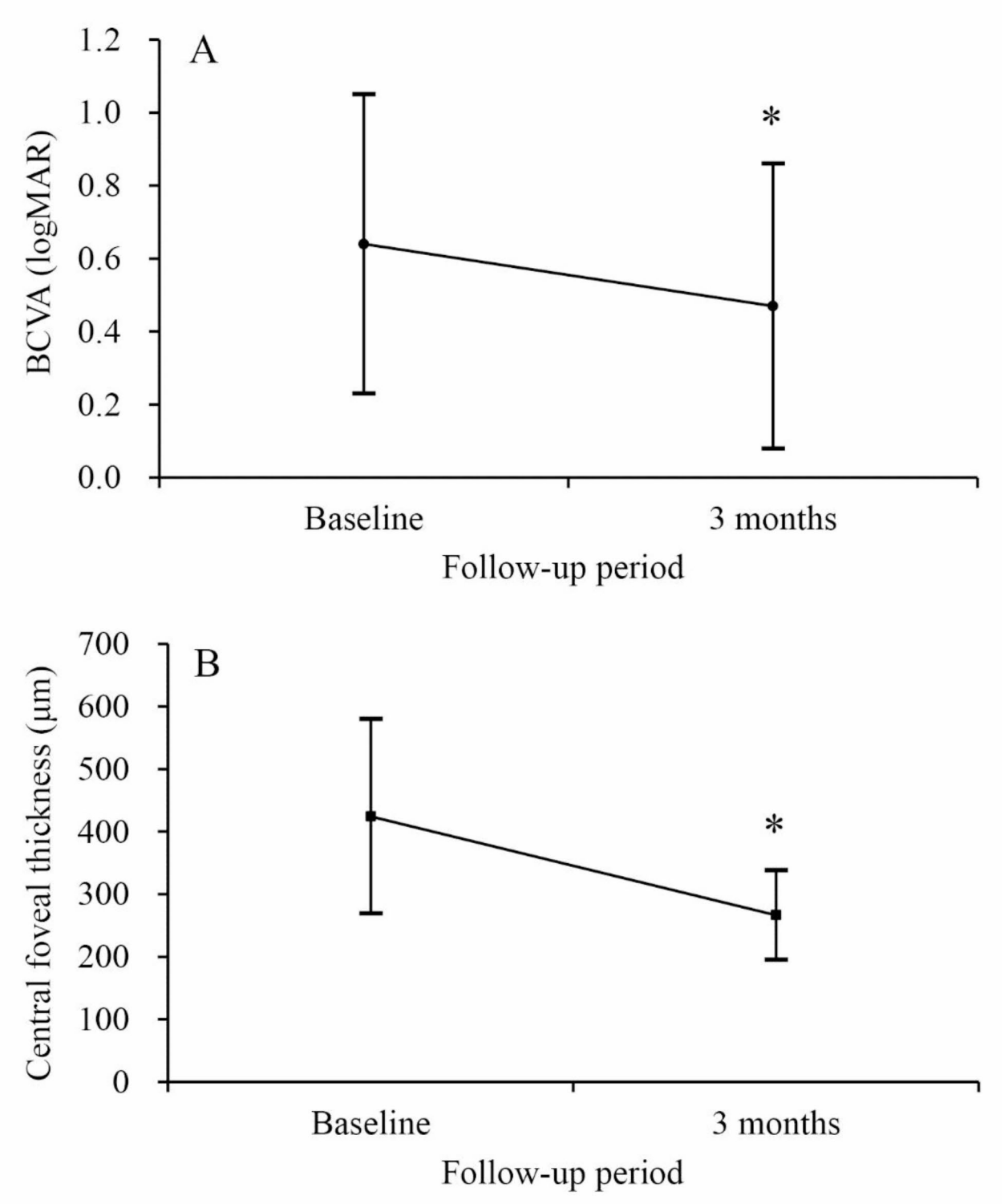

Fig. 1. Changes in (**A**) BCVA and (**B**) CRT after three loading injections of faricimab (3 months). BCVA was significantly improved ($P < 0.001$), and CRT significantly decreased ($P < 0.001$) after treatment. Statistical analysis was performed using paired t-tests. An asterisk indicates a statistically significant difference compared to the baseline value. BCVA, best corrected visual acuity; CRT, central retinal thickness; logMAR, logarithm of minimum angle of resolution.

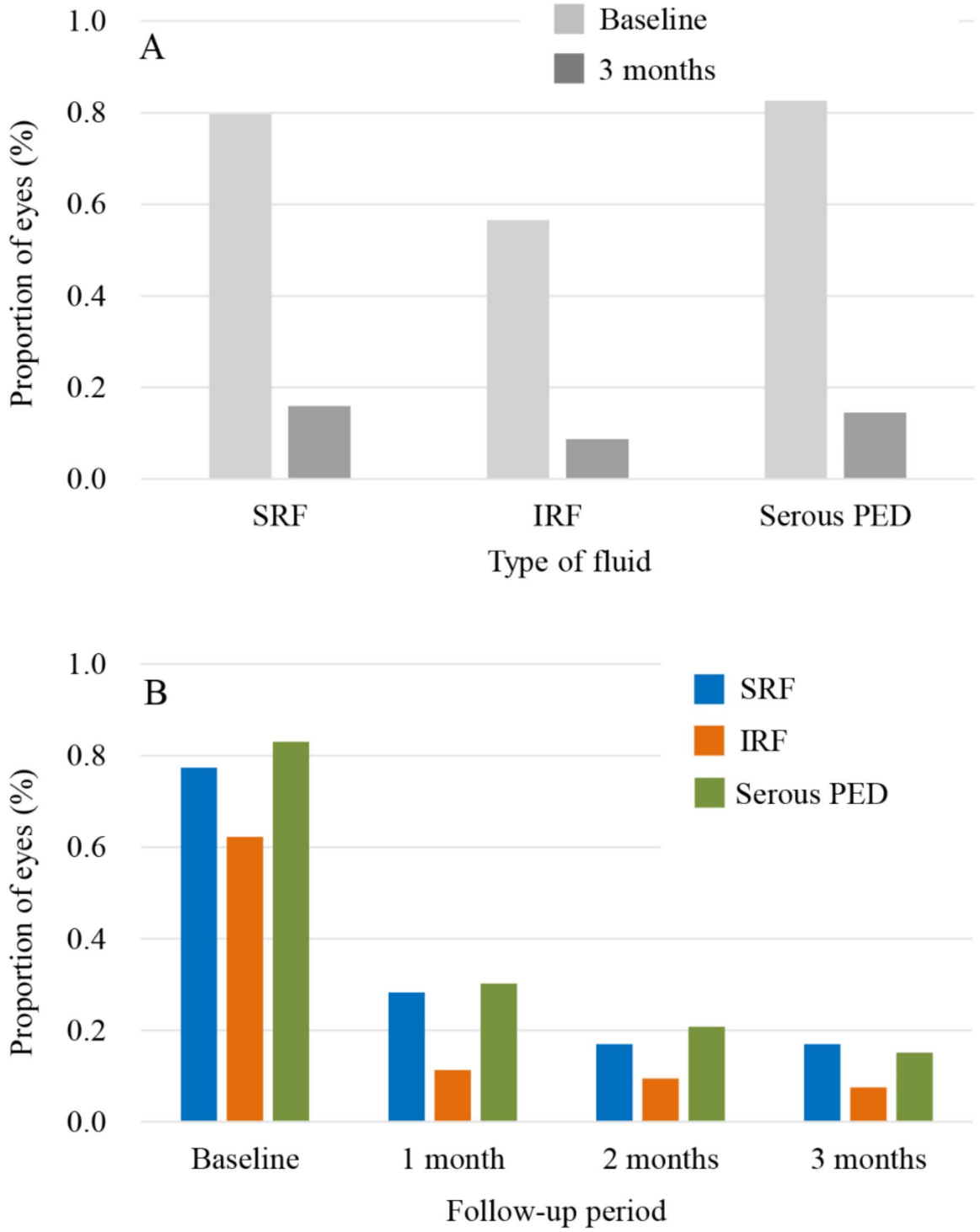

Fig. 2. Changes in the proportion of eyes with pathological findings on optical coherence tomography. (**A**) Changes in the proportion of eyes with SRF, IRF, and serous PED before and after three loading injections ($n = 69$). (**B**) Changes in the proportion of each fluid compartment over the follow-up period ($n = 53$). IRF, intraretinal fluid; PED, pigment epithelial detachment; SRF, subretinal fluid.

After three loading injections of faricimab, the mean decrease in CRT was 145.4 μm, which was significantly greater than the mean decrease of 133.0 μm observed after aflibercept loading injections.

In real-world data studies, Mukai et al. observed that after three loading injections, there was a significant reduction in the incidence of SRF from 87 to 11% along with a decrease in IRF from 36–3%.[11] The study involved

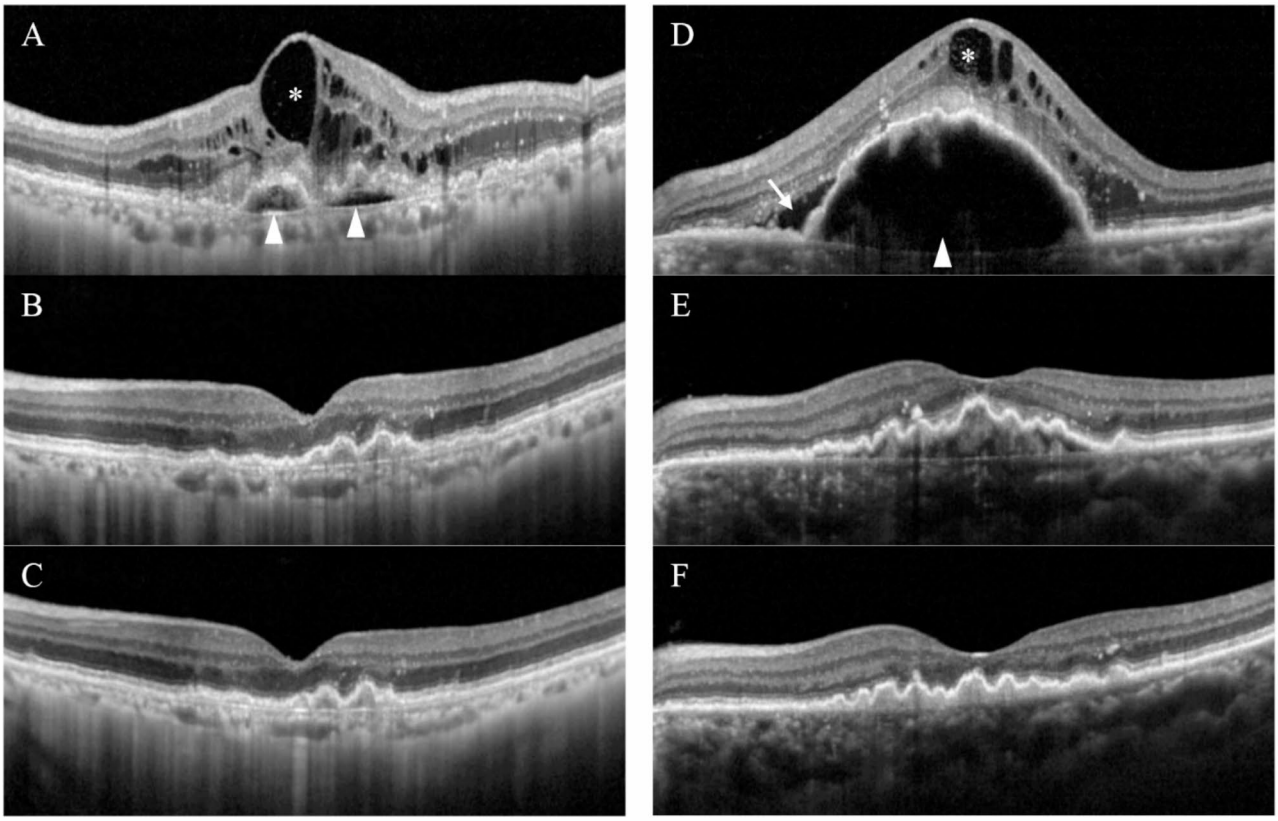

Fig. 3. Representative cases demonstrating the clinical outcomes of three loading injections of faricimab. (**A**–**C**) A 76-year-old patient initially presented with type 2 MNV and received faricimab treatment. (**A**) At diagnosis, OCT revealed IRF (asterisk) and serous PED (arrowheads). (**B**) One month after the first injection, complete resolution of IRF and serous PED was observed. (**C**) The macula remained dry at 3 months. (**D**–**F**) A 77-year-old patient initially presented with type 3 MNV and received faricimab treatment. (**D**) At diagnosis, OCT revealed IRF (asterisk), SRF (arrow), and serous PED (arrowhead). (**E**) One month after the first injection, complete resolution of IRF and SRF was observed, along with a marked decrease in serous PED. (**F**) The macula remained dry at 3 months, with complete resolution of serous PED. IRF, intraretinal fluid; MNV, macular neovascularization; OCT, optical coherence tomography; PED, pigment epithelial detachment; SRF, subretinal fluid.

Characteristics	*P*-value*	β	95% CI
Age	0.464		
Type of macular neovascularization			
Type 1	–		
Type 2	0.029	27.856	1.396–555.957
Type 3	0.048	17.098	1.017–287.591
Central retinal thickness, μm	0.097		
Presence of subretinal fluid	0.460		
Presence of intraretinal fluid	0.239		
Presence of serous PED	0.052		

Table 2. Associations of baseline characteristics with complete resolution of subretinal and intraretinal fluids after three loading injections of faricimab. * Statistical analysis was performed using binary logistic regression. CI, confidence interval; PED, pigment epithelial detachment.

63 eyes, including 22 with PCV[11]. Similarly, in a study by Khanani et al. involving 39 treatment-naïve eyes, a single injection of faricimab resulted in a 40.0% reduction in IRF, a 25.0% reduction in SRF, and a 41.7% reduction in PED[9]. In another study by Matsumoto et al., which involved 40 eyes, the mean foveal thickness decreased from 278 μm at baseline to 173 μm following three loading injections of faricimab[10]. Furthermore, in a study by Tanaka et al., which involved 10 eyes with PCV, 11 eyes with pachychoroid neovasculopathy, and 1

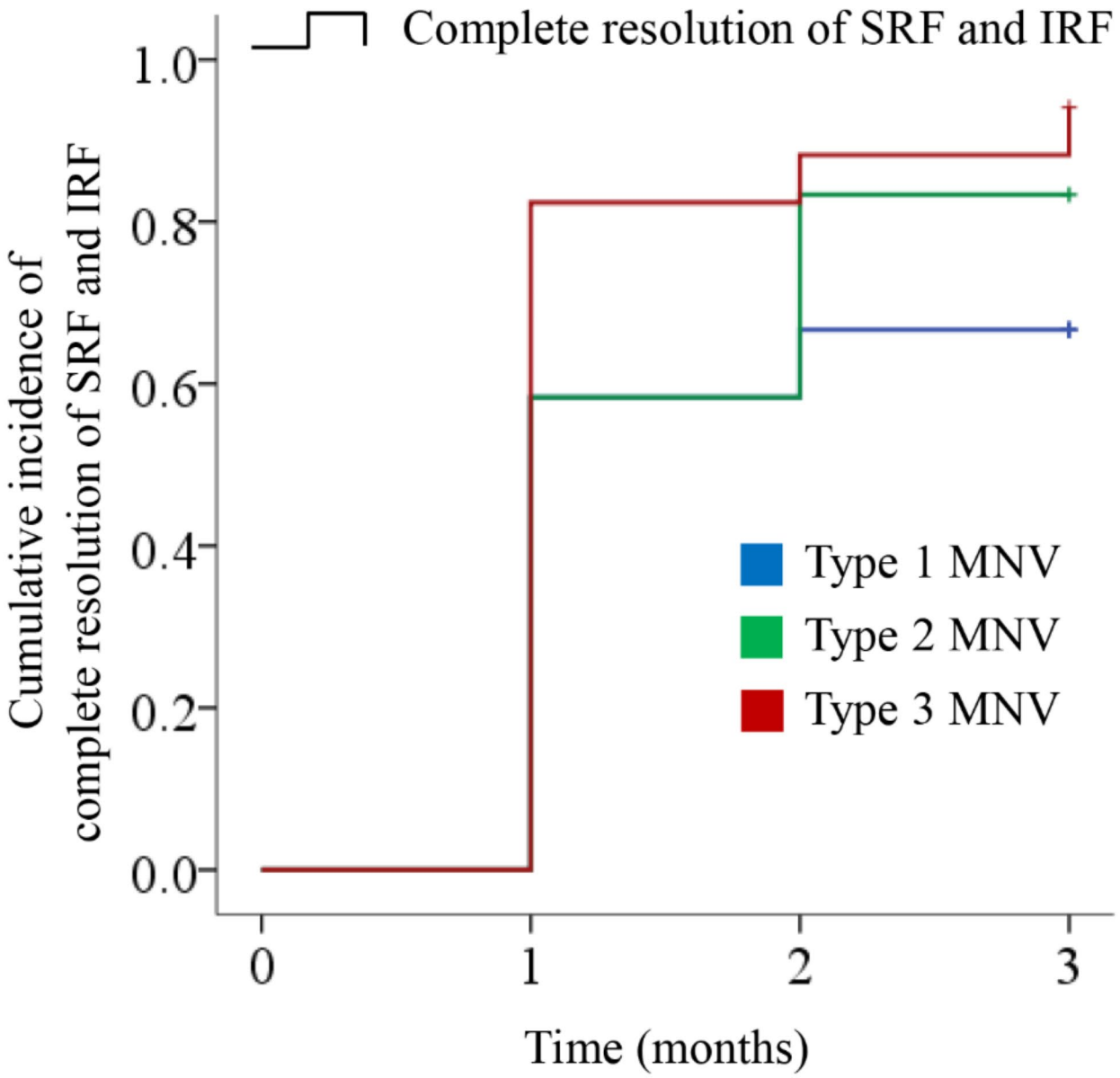

Fig. 4. A Kaplan–Meier graph depicting the cumulative incidence of complete resolution of both SRF and IRF, stratified by MNV type. IRF, intraretinal fluid; MNV, macular neovascularization; SRF, subretinal fluid. The log-rank test revealed no significant difference in complete fluid resolution among the different types of MNV ($P=0.100$).

eye with type 3 MNV, faricimab was effective in both neovascular AMD and PCV, with complete resolution of retinal fluid achieved in 77.3% of cases following three loading injections[12].

The anatomical outcomes of faricimab treatment in our patients are consistent with those reported in previous real-world studies[9–12]. In the treatment of neovascular AMD, the initial three monthly injections are a globally recognized approach. Moreover, whether the fluid is completely resolved after this initial treatment is crucial in clinical practice. Employing an as-needed approach allows for patient monitoring without additional injections[21,22], while a treat-and-extend approach allows for longer intervals between injections[23]. Furthermore, the results of the loading injections serve as an important indicator linked to long-term treatment outcomes, showing that complete fluid resolution correlates with improved long-term results[24,25]. In our study, SRF and IRF were completely resolved in 81.2% of cases after three loading injections of faricimab, slightly exceeding the 77% resolution rate observed in the TENAYA and LUCERNE studies. This finding suggests that faricimab may exhibit excellent anatomical effects even in real-world settings.

In line with the findings of Mukai et al.[11] and Khanani et al.[9], which documented a notable reduction in retinal fluids after just one injection, our study also recorded the resolution of SRF, IRF, or serous PED in nearly half of the patients after a single faricimab injection. These results indicate that faricimab is effective in fluid control.

In the present study, the anatomical effects of faricimab were analyzed according to MNV type, and type 2 and type 3 MNV were found to be associated with complete fluid resolution following faricimab loading injections. The incidence of resolution of both SRF and IRF was 88.2% in type 2 MNV and 94.7% in type 3 MNV, indicating that fluid resolution occurred in nearly all patients. It is well established that type 2 and type 3 MNV demonstrate relatively favorable initial treatment responses, with visual improvement, to anti-VEGF therapy[26]. In particular, complete fluid resolution was achieved in 90.3–94.7% of type 3 MNV cases after three loading injections[27,28]. This rate is comparable to, or slightly lower than, the rate observed in our patients following faricimab treatment. Although the present study did not conduct a direct comparison with other anti-VEGF agents, which limits definitive conclusions, our findings suggest that faricimab may exhibit particularly strong anatomical effects in type 2 and type 3 MNV, supporting its potential as a first-line treatment option for these MNV types. In our patients with type 1 MNV, a high rate of 69.7% showed complete retinal fluid resolution after faricimab treatment, although this rate was slightly lower than that reported by Tanaka et al.[12].

A notable finding of the present study is the high rate of serous PED resolution. After the first injection, the resolution of serous PED occurred rapidly, and by the 3-month mark, serous PED had resolved in a significant 68% of patients. In a study by Khanani et al., a 11.1% reduction in PED was observed following a switch to faricimab in patients previously treated with other anti-VEGF agents[9]. This finding suggests that faricimab may have superior efficacy in resolving PED compared to alternative agents in certain patients. A recent study by Veritti et al. also demonstrated rapid and significant improvement in PED following faricimab treatment[29]. The reduction in PED volume was observed as early as 1 day after treatment, with a decrease of 12%; this reduction further progressed to 29% at 7 days, 51% at 14 days, and 68% at 1 month. Among the various types of PED, the most substantial reduction in PED volume was seen in predominantly serous PED.

Conversely, in the study by Mukai et al., the mean reduction in PED height following faricimab loading injections was 124 μm, which was slightly greater but not significantly different from the reduction observed with aflibercept (mean of 108 μm)[30]. Although recent analyses from the TENAYA and LUCERNE studies reported a greater reduction in PED height in the faricimab treatment group compared to the aflibercept group, further studies are needed to accurately evaluate the effectiveness of faricimab in treating PED.

There are several limitations to the present study. First, it was conducted retrospectively, and no specific criteria for selecting anti-VEGF agents were established. Second, although the total number of patients was not small, the analysis by MNV type included a relatively small number of patients in each subgroup. Third, the study focused solely on the effects of faricimab without comparison to other anti-VEGF agents. Fourth, although the TENAYA and LUCERNE studies used four loading injections of faricimab[7], this study analyzed the results following only three loading injections; the outcomes might have differed if a fourth injection had been administered. Fifth, the analysis excluded patients with PCV, and all patients were of Korean descent. Lastly, all image analyses were conducted by a single examiner. However, comparisons with other examiners demonstrated high levels of agreement, particularly in determining the presence or absence of retinal fluid.

In conclusion, the present study demonstrated significant functional and anatomical improvement following three loading injections of faricimab in treatment-naïve neovascular AMD. In particular, the resolution of SRF, IRF, and serous PED occurred rapidly and at a high rate, with these anatomical effects being especially pronounced in type 2 and type 3 MNV. These findings suggest that the effects of faricimab observed in clinical trials can be successfully replicated in real-world settings.

Data availability

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

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Author contributions

Involved in conception and design (J.H.K.); acquisition of data (H.Y.H., J.H.L., S.M.P., C.G.K., J.W.K., H.J.C., J.H.K.); analysis and interpretation (H.Y.H., J.H.L., S.M.P., C.G.K., J.W.K., H.J.C., J.H.K.); drafting the article (J.H.K., H.Y.H.); revising the article critically for important intellectual content (J. H. K.); and final approval of the article (H.Y.H., J.H.L., S.M.P., C.G.K., J.W.K., H.J.C., J.H.K.). J.H.K. and H.J.C. contributed equally to this work and are considered co–corresponding authors.

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Declarations

Competing interests

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Additional information

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