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Two-year visual and psychological outcomes of ranibizumab and subsequent treatment for diabetic macular oedema in Japan (MERCURY)

Taiji Sakamoto [ID],[1] Masahiko Shimura,[2] Shigehiko Kitano,[3] Masahito Ohji,[4] Yuichiro Ogura,[5,6] Hidetoshi Yamashita,[7] Makoto Suzaki,[8] Kimie Mori,[8] Masanari Kozawa,[8] Poh Sin Yap,[9] Takeumi Kaneko,[8] Tatsuro Ishibashi,[10] for the MERCURY Study Group

ABSTRACT

Objective We report the 2-year visual and psychological outcomes of the MERCURY study, examining the long-term effectiveness and safety of ranibizumab and subsequent therapy in Japanese patients with diabetic macular oedema with impaired visual acuity (VA) in the real-world setting.

Methods and analysis This was a 24-month, phase 4, open-label, single-arm, multicentre, prospective, observational study. Following an initial dose of ranibizumab (0.5 mg) by intravitreal injection (0.05 mL), treatment was administered as needed after month 1. The primary treated eye (PTE) was the first eye that received a ranibizumab injection.

Results In total, 209 patients were enrolled; 192 (91.9%) and 174 (83.3%) completed months 12 and 24, respectively. In the PTE set, mean±SD changes in best-corrected VA (BCVA) from baseline to months 12 (primary endpoint) and 24 were −0.08±0.35 (p=0.015) and −0.13±0.30 (p<0.001) logarithmic minimum angle of resolution, respectively. Mean±SD central subfoveal thickness (CSFT) changes from baseline to months 12 and 24 were −102.3±146.1 µm (p<0.001) and −103.6±157.2 µm (p<0.001), respectively. Patients receiving three injections during the first 2 months had greater BCVA improvements throughout the study than those receiving 1–2 consecutive injections. Overall, 91 (43.5%) and 130 (62.2%) patients had ocular and non-ocular adverse events, respectively. At month 24, the mean±SD Hospital Anxiety and Depression Scale (HADS)-Anxiety and HADS-Depression scores decreased by 0.44±3.75 (p=0.196) and 0.19±3.38 (p=0.541), respectively.

Conclusions At 24 months after initiation of ranibizumab and subsequent treatment, patients showed significant BCVA and CSFT improvements. Long-term treatment was considered safe and tolerable and did not lead to worsened psychological status.

INTRODUCTION

Both globally and in Japan, diabetes is among the most common endocrine disorders, and its prevalence is expected to continue to increase worldwide.[1] In Japan, the prevalence of diabetes among individuals between 20 and 79 years of age was estimated in 2021 to be 11.8%, accounting for approximately 11 million persons.[2]

The goal of diabetes treatment is to prevent or delay complications and optimise patients' quality of life.[3] Nevertheless, a sizeable proportion of patients develop complications during the disease course, including diabetic retinopathy (DR), which is one of the main causes of vision loss globally[4] and has been associated with a considerable burden on patients and healthcare systems in Japan.[5] DR is also a common

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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Studies show that the antivascular endothelial growth factor (anti-VEGF) drug ranibizumab is effective for diabetic macular oedema (DME); however, more information is needed on optimal long-term anti-VEGF treatment in real-world settings and its effects on patients' psychological status.

⇒ Following promising 12-month interim results of the MERCURY study on the long-term effectiveness and safety of ranibizumab in Japanese patients with DME, we report here the 2-year visual and psychological outcomes of the MERCURY study.

WHAT THIS STUDY ADDS

⇒ Patients experienced significant improvements in best-corrected visual acuity and central subfoveal thickness, and no worsening of anxiety or depression, at 12 and 24 months when three injections were given in the first 2 months.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings indicate that three injections of ranibizumab during the first 2 months of treatment is efficacious and safe for patients with DME in real-world settings.

cause of vision loss among adults of working age in Japan (≥30 years), most commonly affecting adults aged 50–69 years.[6]

Diabetic macular oedema (DME) is the leading cause of retinopathy-associated visual impairment in patients with diabetes mellitus. A recent epidemiological study of ocular complications related to diabetes mellitus in Japan, along with diabetic neuropathy and diabetic nephropathy, included over 66000 diabetes mellitus patients registered in a Japanese claims database and reported that DR was the most frequent complication of diabetes mellitus (23.6%).[7] Although the frequency of ocular complications other than DME was reduced over time, the frequency of DME significantly increased during the study.[7] DME can occur at any stage of DR. It has been associated with persistent hyperglycaemia, inflammation and vascular endothelial dysfunction,[8] and is characterised by central macular thickening and vision loss if untreated.[9]

The mainstay of DME treatment is antivascular endothelial growth factor (VEGF) therapy.[6 10 11] Other treatments include conventional laser photocoagulation, vitrectomy and steroid therapy.[6] DME management should address visual acuity (VA) impairment and care for the patient's quality of life and psychological status.

Ranibizumab is a recombinant, humanised monoclonal antibody fragment that neutralises all active forms of VEGF-A[12] and prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells. As a result, endothelial cell proliferation, vascular leakage and new blood vessel formation are reduced.[13] Randomised phase 3 studies on the efficacy of intravitreal ranibizumab injections, either as monotherapy or in combination with laser treatment, showed that ranibizumab treatment was more effective for DME than laser treatment alone at 1 year.[14]

Standard criteria regarding optimal long-term treatment with anti-VEGF agents and frequency of injections in the real-world setting are lacking. Further, the long-term effects of DME treatment on the psychological status of patients have not been thoroughly evaluated using specific psychological measures.

The MERCURY study examined the long-term effectiveness and safety of ranibizumab and subsequent therapy in Japanese patients with DME with impaired VA and evaluated the psychological effects associated with expected outcomes (VA improvements) after anti-VEGF treatment in patients with DME in the real-world setting. The 12-month interim results have been published,[15] and after 12 months of treatment, the mean best-corrected VA (BCVA) had significantly improved, and while patients' depression scores had not improved, they had significantly decreased anxiety scores. Here, we report the 2-year visual and psychological outcomes of the MERCURY study, evaluating ranibizumab and subsequent treatment for DME in Japan.

MATERIALS AND METHODS
Study design, treatment and data collection
The MERCURY study was a 24-month, phase 4, open-label, single-arm, multicentre, prospective, observational study conducted in Japan from April 2017 to December 2020.[15] Data were collected using electronic case report forms, and patients were discontinued from the study if they had not attended ophthalmology study visits at least once a year, withdrew consent or for other reasons.

The study treatment dose, frequency and duration were based on the Japanese ranibizumab package insert.[12] An initial dose of ranibizumab (0.5 mg) was administered by intravitreal injection (0.05 mL) and subsequently was administered as needed after month 1. Patients could receive other ocular anti-VEGF agents from the second injection at the investigator's discretion. There were no restrictions regarding additional adjunctive treatments.

The primary treated eye (PTE) was the first eye that received a ranibizumab injection. If the other eye also underwent an injection of ranibizumab, it was referred to as the secondary treated eye (STE). If both eyes were treated on the same date, the eye with the earliest diagnosis date was considered the PTE. If both eyes had the same diagnosis date, the investigator chose one eye as the PTE.

Institutional review boards approved the study protocol at each centre (online supplemental table S1), and the study was conducted following the principles of the Declaration of Helsinki, and guidelines for Good Clinical Practice, Good Post-marketing Study Practice and Good Pharmacoepidemiology Practices. All participants provided written informed consent. The study was registered at Japan Pharmaceutical Information Center-Clinical Trials Information under the identifier number JapicCTI-173610.

Patients
The main inclusion criteria were age ≥20 years, DME, impaired VA according to the investigator, no previous intravitreal or systemic anti-VEGF agents, a plan to initiate ranibizumab intravitreal injections and attendance at study visits for at least 12 months. Patients were excluded if they were participating in other clinical trials, if they were planned to undergo systemic anti-VEGF agents within 12 months from study initiation, and if they had a contraindication such as hypersensitivity to ranibizumab or its excipients, a confirmed or suspected infection, or inflammation in or in proximity to the eye.

Study outcomes
The primary outcome was the effectiveness of treatment based on the mean change in BCVA in the logarithmic minimum angle of resolution (logMAR) from baseline to month 12. Secondary outcomes were monthly changes in BCVA in logMAR and central subfoveal thickness (CSFT) measured by optical coherence tomography over 24 months, the mean change in BCVA in logMAR from baseline to month 24 in patients who received three or

1–2 anti-VEGF injections during the first 2 months, and safety based on adverse events (AEs) coded according to the Medical Dictionary for Regulatory Activities V.22.0. The investigators judged whether AEs were study drug related.

The psychological status of patients was assessed in an exploratory manner at baseline and months 3, 12 and 24 using the Japanese translation of the Hospital Anxiety and Depression Scale (HADS).[16 17] The HADS questionnaire includes 14 items for depression and anxiety (seven items for each subscale). Each item is scored from 0 (no impairment) to 3 (severe impairment), with 21 being the maximum score for depression or anxiety. Total subscale scores of 8–10, 11–14 and 15–21 indicate mild, moderate and severe depression or anxiety, respectively.[18] The relationships between HADS-Anxiety (HADS-A) and BCVA of the better eye (BE) (BE BCVA), and between HADS-A and the number of anti-VEGF injections were also evaluated to determine the impact of DME treatment on the HADS-A score. Eyes were classified as the BE, worse eye or as having vision equivalent to the other eye according to the baseline BCVA data in both eyes.

Statistical analysis
Details of the statistical analyses have been published previously.[15] The target sample size was 200 patients based on the results of previous studies.[14 19] Descriptive statistics were used for analysis, and estimates and corresponding 95% CIs were calculated. A paired t-test was used to compare mean changes, and the χ^2 test was used to compare categorical variables. Pearson's correlation coefficient was used to assess the correlation between continuous variables. All analyses were conducted based on the observed data, and no imputation method was applied. A p-value of <0.05 was determined to be statistically significant. All analyses were conducted using SAS V.9.4 (SAS Institute).

Patient and public involvement
When the study was conducted, patient advocacy groups had not been established. Therefore, patients and the public were not involved in the design and conduct of the study, selecting outcome measures or recruitment of participants.

RESULTS
Patient characteristics
In total, 209 patients were enrolled, among whom 192 (91.9%) completed month 12 and 174 (83.3%) completed month 24. Thirty-five patients (16.8%) discontinued the study for the following reasons: consent withdrawal (n=19), not attending ophthalmology study visits at least once a year (n=8), death (n=6), and protocol deviation and administrative issue (n=1 each).

Patients had a mean age of 64.4 years, and 61.7% (129/209) of patients were male (table 1). The mean body mass index was 24.5 kg/m², and mean glycated haemoglobin (HbA1c) was 7.29%. At baseline, the mean
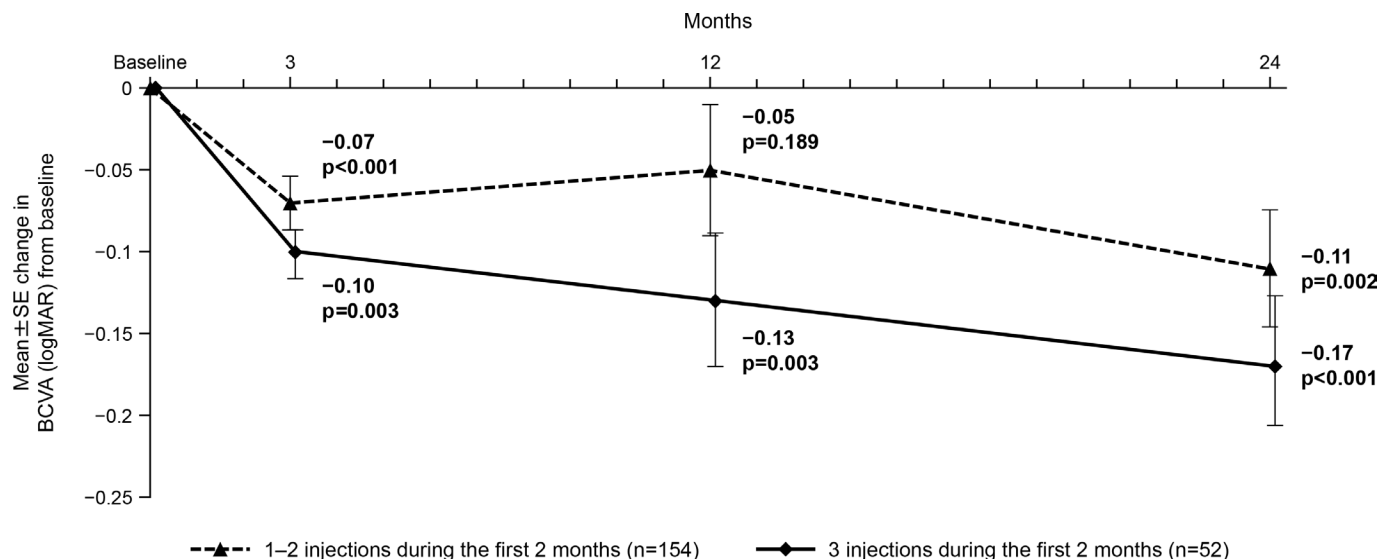
Table 1 Baseline patient demographics and disease and ocular characteristics (PTE set)

Variable	PTE, N=209
Age (years), mean±SD	64.4±12.8
Male, n (%)	129 (61.7)
Body mass index (kg/m²), mean±SD (n=166)	24.5±3.6
HbA1c (%), mean±SD (n=140)	7.29±1.28
BCVA (logMAR), mean±SD	0.43±0.39
CSFT (µm), mean±SD (n=203)	459.0±138.7
Bilateral DME, n (%)	123 (58.9)
Prior DME treatment, n (%)	121 (57.9)
PDR, n (%)	69 (33.0)
Lens status (phakic), n (%)	124 (59.3)
Medical history/comorbidities, n (%)	
Type 1 diabetes	4 (1.9)
Type 2 diabetes	205 (98.1)
Dyslipidaemia	106 (50.7)
Hypertension	131 (62.7)
HADS score, mean±SD (n=206)	
HADS-Anxiety	4.26±3.79
HADS-Depression	4.67±4.22
HADS-Anxiety score ≥8, n (%)	37 (18.0)
HADS-Depression score ≥8, n (%)	41 (19.9)

BCVA, best-corrected visual acuity; CSFT, central subfoveal thickness; DME, diabetic macular oedema; HADS, Hospital Anxiety and Depression Scale; HbA1c, glycated haemoglobin; logMAR, logarithmic minimum angle of resolution; PDR, proliferative diabetic retinopathy; PTE, primary treated eye.

BCVA (logMAR) was 0.43 (equivalent to 63.5 early treatment diabetic retinopathy study (ETDRS) letters) and the mean CSFT was 459.0 µm. The proportion of patients with proliferative DR was 33.0% (69/209).

Treatment exposure
In total, 209 patients had a PTE; of these, 64 had an STE (30.6%). The mean±SD numbers of anti-VEGF treatments (including ranibizumab) from baseline to month 23 were 4.9±3.9 and 4.2±3.5 in the PTE and STE sets, respectively. During the same period, the mean (±SD) numbers of ranibizumab injections were 4.1±3.3 and 3.1±2.6 in the PTE and STE sets, respectively. At month 23, a total of 94 (45.0%) and 26 (40.6%) eyes had received DME adjunctive therapy in the PTE and STE sets, respectively. Thirty-five (16.8%) and 9 (14.1%) patients had received focal/grid laser photocoagulation, 35 (16.8%) and 7 (10.9%) intraocular steroid injection, 47 (22.5%) and 14 (21.9%) panretinal photocoagulation, 13 (6.2%) and 6 (9.4%) vitrectomy, and 6 (2.9%) and 2 (3.1%) other treatments in the PTE and STE sets, respectively.

Figure 1 Mean (±SE) change in BCVA (logMAR) from baseline to month 24 according to the number of anti-VEGF injections administered during the first 2 months (PTE set). Mean BCVA (logMAR) values at baseline were 0.43 both in patients who received 1–2 injections from baseline to month 2 and in patients who received three injections from baseline to month 2. In patients who received 1–2 injections from baseline to month 2, the mean number of total injections was 4.0. In patients who received three injections from baseline to month 2, the mean number of total injections was 7.7. P values were calculated using the paired t-test versus baseline values. A total of 206 patients had BCVA data from the PTE both at baseline and post-baseline; 3 out of 209 patients did not have BCVA data from the PTE at post-baseline. BCVA, best-corrected visual acuity; logMAR, logarithmic minimum angle of resolution; NA, not applicable; PTE, primary treated eye; VEGF, vascular endothelial growth factor.

Study outcomes

Effectiveness

In the PTE set, the mean±SD change in BCVA from baseline to month 12 was −0.08±0.35 logMAR (p=0.015) and to month 24 was −0.13±0.30 logMAR (p<0.001). The proportion of patients achieving BCVA improvements of ≤−0.3 logMAR units from baseline to month 12 was 12.0% (15/125) and from baseline to month 24 was 24.8% (29/117) in the PTE set. Significant differences in CSFT changes from baseline were recorded after 12 months (−102.3±146.1 µm; p<0.001) and 24 months (−103.6±157.2 µm; p<0.001) in the PTE set.

VA outcomes and treatment frequency

In the PTE set, those receiving three injections during the first 2 months had greater BCVA improvements throughout the study (from baseline to month 24) than those receiving only one or two consecutive injections (figure 1). In subgroups of patients stratified by the number of anti-VEGF injections received during the study, all subgroups of those who initially (first 2 months of treatment) received three injections showed significant improvements in BCVA changes, which was not the case for all subgroups of patients initially treated with one or two injections (figure 1).

Safety

Overall, 91 patients (43.5%) had ocular AEs and 130 patients (62.2%) had non-ocular AEs. In the safety set, 28 patients (13.4%) presented ocular serious AEs (SAEs), of which one event of vitreous haemorrhage was suspected to be related to ranibizumab. The most common ocular SAEs were vitreous haemorrhage (12 (5.7%)) and glaucoma (7 (3.3%)). In total, 57 patients (27.3%) reported non-ocular SAEs, of which three events (two cerebral infarctions and one dizziness) were suspected to be related to ranibizumab. The most common non-ocular SAEs were diabetic nephropathy (6 (2.9%)) and cerebral infarction (5 (2.4%)). Six deaths were reported during the study, but none were suspected to be related to ranibizumab. The causes of death were cardiac failure, acute cardiac failure, suicidal behaviour, myocardial infarction and rectal cancer (one each). The cause of death was unknown in one case.
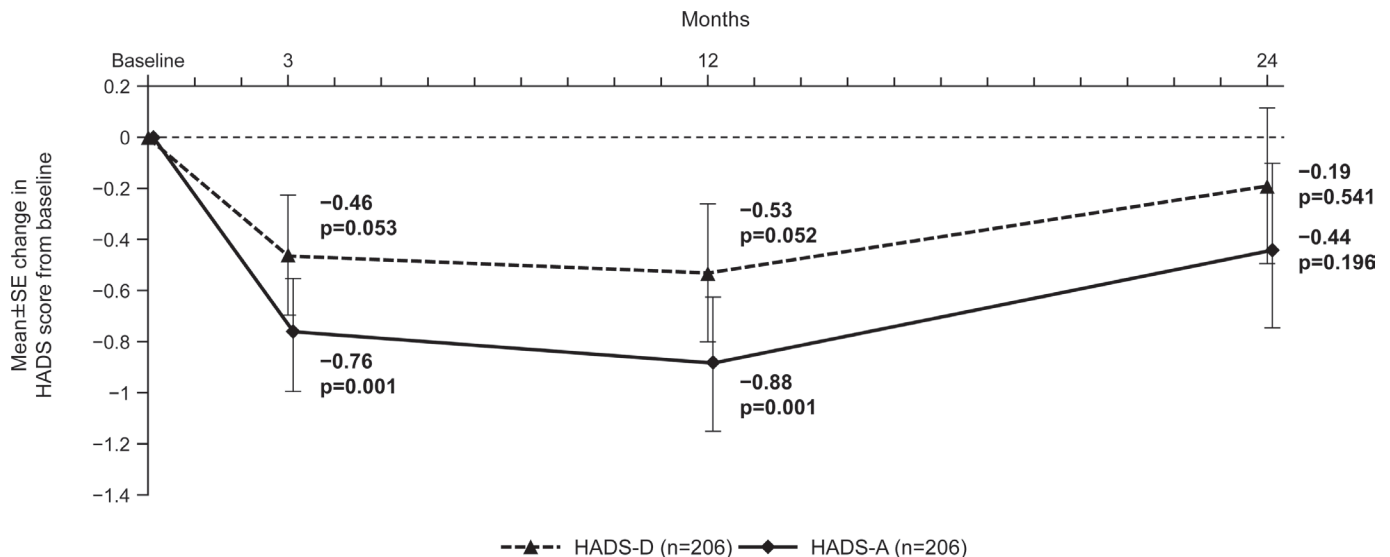
Figure 2 Mean (±SE) change in HADS scores from baseline (safety set). P values were calculated using the paired t-test versus baseline values. HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS-Anxiety subscale; HADS-D, HADS-Depression subscale.

Exploratory outcomes

Figure 2 shows the mean changes in HADS score from baseline to month 24. At months 3, 12 and 24, the mean (±SD) HADS-A scores decreased by 0.76±2.81 (p=0.001), 0.88±3.09 (p=0.001) and 0.44±3.75 (p=0.196), respectively. At months 3, 12 and 24, the HADS-Depression (HADS-D) scores decreased from baseline by 0.46±3.16 (p=0.053), 0.53±3.26 (p=0.052) and 0.19±3.38 (p=0.541), respectively.

Of the 209 eyes in the PTE set at baseline, 44 (21.1%) were classified as the BE, 131 (62.7%) were classified as the worse eye and 25 (12.0%) were considered to have vision equivalent to the other eye. Nine eyes (4.3%) were not classified due to a lack of baseline BCVA data in the other eye. For the 64 eyes in the STE set, 36 (56.3%) were classified as the BE, 16 (25.0%) were classified as the worse eye, and 12 (18.8%) were considered to have vision equivalent to the other eye. After the DME treatment to both eyes, BE BCVA (logMAR) improved from baseline (0.21±0.34) to month 12 (−0.07±0.26; p=0.008) and month 24 (−0.06±0.19; p=0.001). Changes in the BE BCVA were evaluated according to HADS-A score (improved or maintained/deteriorated) and they significantly improved from baseline to month 24 in the improved group (−0.09±0.20; p=0.006) but not in the maintained/deteriorated group (−0.05±0.19; p=0.089).

The relationships between HADS-A and BE BCVA and between HADS-A and the number of anti-VEGF injections were evaluated. Patients with a HADS-A change of ≤−1 from baseline to month 24 showed a significant decrease in BE BCVA (mean±SD −0.09±0.20 logMAR, p=0.006) but those with a HADS-A change of >−1 from baseline to month 24 did not (mean±SD −0.05±0.19 logMAR, p=0.089). No correlation was found between the number of anti-VEGF injections in both eyes from baseline to month 23 and the changes in HADS-A score from baseline to month 24.

DISCUSSION

The MERCURY study was a real-world, observational analysis of Japanese patients with DME and impaired VA that assessed the effectiveness and safety of ranibizumab and subsequent therapy. The mean BCVA (logMAR) and CSFT values were significantly improved (both p<0.001) at 24 months after initiation of ranibizumab treatment. As the impact of long-term treatment with intravitreal injections on the psychological status of patients with DME has not been thoroughly assessed, an exploratory analysis was conducted during the 24-month study to evaluate this effect. This study may be the first to assess the psychological effects of 2-year anti-VEGF treatments for DME using a specific psychological measure, the HADS. The analysis showed non-significant decreases in the scores for both HADS-A and HADS-D.

The mean BCVA gain (mean change −0.13 logMAR, equivalent to +6.5 ETDRS letters) achieved at month 24 in MERCURY is comparable with the results of other real-world studies.[20–24] The BCVA gains and proportion of patients with BCVA improvement at month 24 were slightly higher than those at month 12, but the BCVA gains at month 24 were markedly less than those reported in previous randomised controlled trials (+7.24 ETDRS letters at month 6 in the READ study; +10.3 ETDRS letters at month 12 in the RESOLVE study; and improved >15 ETDRS letters in 33.6%–45.7% of patients at month 24 in the RISE and RIDE studies).[14] However, these findings align with the results of a previous report in which intravitreal injections tended to be less frequent in real-world practice,[25] which could have led to reduced effectiveness than randomised trials,[26] where treatment

administration was likely more stringent. Difficulty in achieving adequate anti-VEGF treatment in the real-world setting in Japan may be due to the costs of therapy, frequency of injections and other ocular complications.[27] Of note, the standard treatment involves three injections administered 4 weeks apart for most labels of ranibizumab, which is in line with the regimen used in clinical trials.[28 29] The relatively lower frequency of injections reported in this study compared with that in other studies conducted overseas was because of differences in study types (real-world observational study vs clinical trials).

Patients who received fewer anti-VEGF agent injections in the first 2 months of treatment had a worse visual prognosis than those receiving three injections initially, regardless of the number of injections received throughout the study. Thus, a higher number of monthly injections during the first 2 months of treatment may result in a greater benefit.

All subgroups of patients receiving three injections during the first 2 months of treatment had significantly improved BCVA at month 24 compared with those who did not. Although the beneficial impact of this treatment regimen on BCVA at month 12 has been suggested previously,[15 22] this is the first study to show the impact that three initial monthly ranibizumab injections might still have on BCVA at month 24 in the clinical setting.

The psychological status of the patients in this study was maintained during the 2-year anti-VEGF agent treatment. We have shown a relationship between the BE BCVA and HADS-A score due to BE BCVA improvements stratified by HADS-A score change, consistent with a previous study.[15 30 31] However, although HADS-A scores significantly improved up to month 12, the mean HADS-A score change at month 24 did not improve. Hasan *et al* reported that diabetes was significantly associated with a 30-day episode of any anxiety disorder (OR 1.53, 95% CI 1.09 to 2.15) in a 27-year longitudinal study of 2791 women with or without diabetes.[32] Diabetes and other diabetic complications may have contributed to a deterioration in the HADS-A score throughout the study despite the initial improvements at months 3 and 12. Unfortunately, we could not investigate the relationship between HADS-A score change and the changes of systemic factors, such as HbA1c, in the study due to the lack of follow-up data. Conversely, Rees *et al*[33] and the 12-month MERCURY report[15] indicated that 18.0%–24.3% and 16.3%–19.9% of patients with DME had HADS-A and HADS-D scores of ≥8, respectively. This means that anxiety and depression are not uncommon in patients with DME. However, the fact that long-term DME treatment initiated with ranibizumab improved VA could have been the reason that the psychological status of these patients did not deteriorate in the real-world setting and, thus, this could be viewed as a positive result.

This 24-month analysis of the MERCURY study has some limitations, including the observational study design, lack of a comparator, limited generalisability as only Japanese patients were included, the use of a questionnaire-based score to measure psychological symptoms, and the loss of patients at 24 months (35/209, 16.7%). Data on systemic factors such as HbA1c, systolic and diastolic blood pressure, triglyceride levels and low-density lipoprotein cholesterol levels, among others, were limited at post-baseline. Therefore, we did not analyse the relationship between changes in systemic factors and the HADS score. Substantial variability was found in the results across patients in our exploratory analysis, as indicated by the large error bars; previous studies described such variability in patient-reported outcomes.[19 34] The challenges associated with using psychological questionnaires such as HADS to show statistically significant changes in mental symptoms according to treatment or between groups cannot be denied.

In conclusion, at 24 months after initiation of ranibizumab and subsequent treatment, patients in the MERCURY study showed significant improvements in BCVA and CSFT, and the long-term treatment was considered safe and tolerable, which confirms previous findings. Long-term treatment initiated with ranibizumab intravitreal injections did not lead to a worsened psychological status of Japanese patients with DME and impaired VA.

Author affiliations
[1]Department of Ophthalmology, Kagoshima University, Kagoshima, Japan
[2]Department of Ophthalmology, Tokyo Medical University Hachioji Medical Center, Hachioji, Japan
[3]Diabetes Center, Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan
[4]Department of Ophthalmology, Shiga University of Medical Science, Otsu, Japan
[5]Genentech Inc, South San Francisco, California, USA (present affiliation)
[6]Department of Ophthalmology and Visual Science, Nagoya City University, Nagoya, Japan
[7]Department of Ophthalmology and Visual Sciences, Yamagata University, Yamagata, Japan
[8]Medical Division, Novartis Pharma K.K., Minato-ku, Tokyo, Japan
[9]Novartis Corporation Sdn. Bhd, Selangor, Malaysia
[10]Kyushu University, Fukuoka, Japan

ORCID iD
Taiji Sakamoto http://orcid.org/0000-0003-0287-3801

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