OPEN ACCESS

Real-world management of treatment-naïve diabetic macular oedema in Japan: two-year visual outcomes with and without anti-VEGF therapy in the STREAT-DME study

Masahiko Shimura ,[1] Shigehiko Kitano,[2] Daisuke Muramatsu,[3] Harumi Fukushima,[2] Yoshihiro Takamura,[4] Makiko Matsumoto,[5] Masahide Kokado,[6] Jiro Kogo,[7] Mariko Sasaki,[8] Yuki Morizane,[9] Osamu Kotake,[10] Takashi Koto,[11] Shozo Sonoda,[12] Takao Hirano,[13] Hiroto Ishikawa,[14] Yoshinori Mitamura ,[15] Fumiki Okamoto,[16] Takamasa Kinoshita,[17] Kazuhiro Kimura,[18] Masahiko Sugimoto,[19] Kenji Yamashiro ,[20] Yukihiko Suzuki,[21] Taiichi Hikichi,[22] Noriaki Washio,[23] Tomohito Sato,[24] Kishiko Ohkoshi,[25] Hiroki Tsujinaka,[26] Sentaro Kusuhara,[27] Mineo Kondo,[19] Hitoshi Takagi,[7] Toshinori Murata,[13] Taiji Sakamoto,[12] On behalf of Japan Clinical Retina Study (J-CREST) group

For numbered affiliations see end of article.

Correspondence to
Professor Masahiko Shimura, Department of Ophthalmology, Tokyo Medical University Hachioji Medical Center, Hachioji 1930998, Japan; masahiko@v101.vaio.ne.jp

Received 4 September 2019
Revised 12 November 2019
Accepted 16 November 2019

To cite: Shimura M, Kitano S, Muramatsu D, *et al. Br J Ophthalmol* 2020;**104**:1209–1215.

ABSTRACT

Background/Aims To investigate real-world outcomes for best-corrected visual acuity (BCVA) after 2-year clinical intervention for treatment-naïve, centr-involving diabetic macular oedema (DME).

Methods Retrospective analysis of longitudinal medical records obtained from 27 institutions specialising in retinal diseases in Japan. A total of 2049 eyes with treatment-naïve DME commencing intervention between 2010 and 2015 who were followed for 2 years were eligible. Interventions for DME included anti-vascular endothelial growth factor (VEGF) therapy, local corticosteroid therapy, macular photocoagulation and vitrectomy. Baseline and final BCVA (logMAR) were assessed. Eyes were classified by the treatment pattern, depending on whether anti-VEGF therapy was used, into an anti-VEGF monotherapy group (group A), a combination therapy group (group B) and a group without anti-VEGF therapy (group C).

Results The mean 2-year improvement of BCVA was −0.04±0.40 and final BCVA of >20/40 was obtained in 46.3% of eyes. Based on the treatment pattern, there were 427 eyes (20.9%) in group A, 807 eyes (39.4%) in group B and 815 eyes (39.8%) in group C. Mean improvement of BCVA was −0.09±0.39, −0.02±0.40 and −0.05±0.39, and the percentage of eyes with final BCVA of >20/40 was 49.4%, 38.9%, and 52.0%, respectively.

Conclusion Following 2-year real-world management of treatment-naïve DME in Japan, BCVA improved by 2 letters. Eyes treated by anti-VEGF monotherapy showed a better visual prognosis than eyes receiving combination therapy. Despite treatment for DME being selected by specialists in consideration of medical and social factors, a satisfactory visual prognosis was not obtained, but final BCVA remained >20/40 in half of all eyes.

INTRODUCTION

Diabetic macular oedema (DME) is one of the leading causes of vision-threatening complications associated with diabetic retinopathy in persons of working age, with an estimated 21 million individuals being affected worldwide.[1] DME can occur at any stage of diabetic retinopathy, and is a major cause of visual impairment in patients with diabetes.[2] The pathophysiology of DME is complex and involves multiple pathways that lead to central macular thickening and loss of vision if treatment is not provided.[3] Several methods have been suggested for treatment of DME. In the 1980s, laser photocoagulation was established as the standard treatment for DME,[4] and vitrectomy was introduced in the 1990s.[5] Subsequently, intravitreal[6] or posterior subtenon[7] injection of triamcinolone acetonide (TA) was found to be effective for DME in the 2000s. In recent years, treatment of DME has been changed markedly by development of anti-vascular endothelial growth factor (VEGF) agents.[8] Repeated administration of anti-VEGF agents for 2 years can improve visual acuity (VA) in patients with DME by 8–12 letters,[9 10] which is a better visual outcome than that achieved with other treatments, and most physicians currently consider anti-VEGF therapy to be first-line treatment for DME. However, anti-VEGF therapy requires monthly visits for injections and one-third of patients show a limited response, with vision decreasing by >15 letters in 5% of eyes. Moreover, it is expensive and compliance is problematic.[11] Therefore, in the real-world clinical setting, retinal experts make efforts to choose the best treatment for each patient in consideration of various medical and social factors.

A retrospective, large-scale multicentre study was performed to investigate the 2-year visual prognosis of treatment-naïve, center-involving DME managed by retina specialists in Japan. Treatment patterns

were classified by the use of anti-VEGF agents and the visual prognosis achieved with each method was determined.

METHODS

The Survey of Treatment for DME (STREAT-DME) database contained longitudinal medical records for a demographically and geographically diverse patient population obtained from 41 retina specialists at 27 institutions in Japan. This retrospective observational study included all eligible patients who received a diagnosis of center-involving DME, started initial treatment between January 2010 and December 2015 and were followed for 2 years (22–26 months). Baseline clinical data obtained from the medical record of each patient included the age, gender, duration of diabetes, glycohaemoglobin and estimated glomerular filtration rate calculated from the creatinine level at initiation of treatment. The best-corrected visual acuity (BCVA) determined with a decimal chart and the central macular thickness (CMT) measured by optical coherence tomography (OCT) at the initial and final visits were also extracted from the database. Interventions for each eye during the 2-year period were determined. DME was diagnosed at each institution, and the timing of treatment was decided by each attending physician.

Treatment for DME was classified as follows: (1) anti-VEGF agents (intravitreal bevacizumab (IVB: 1.25 mg/0.05 mL), ranibizumab (IVR: 0.5 mg/0.05 mL) or aflibercept (IVA: 2.0 mg/0.05 mL)), (2) local corticosteroid (TA therapy (intravitreal TA (IVTA: 4 mg/0.1 mL) or subtenon TA (STTA: 20 mg/0.5 mL)), (3) laser photocoagulation of the macular region and (4) vitrectomy. If cataract surgery was performed or laser photocoagulation outside the macular region was done to prevent retinal ischaemia during the 2-year period, this was also recorded because it could influence the visual prognosis.

Clinical evaluation

To facilitate data analysis, decimal BCVA data were converted to logMAR values or ETDRS equivalent letter scores, as appropriate. Improvement of BCVA was determined by subtracting the final BCVA from the baseline BCVA. If BCVA increased by >0.3 logMAR (15 letters), this was defined as 'improved', while deterioration by >0.3 logMAR was defined as 'worsened'. The proportion of eyes with each prognosis was calculated.

The goal of treating DME is to keep useful BCVA, so the percentage of eyes with a final BCVA better than 0.3 logMAR (20/40 or more on a Snellen chart) was also calculated, since this represents socially useful vision and is defined as 'good' VA, in contrast, BCVA worse than 0.3 logMAR was defined as 'poor' VA.

There are various types of OCT and OCT which was used in each facility was not the same. In this study, OCT data obtained from the same model in each facility were adopted, thus statistically, absolute values should be handled with care. Improvement of CMT was assessed by subtraction of final CMT from baseline CMT.

Treatment patterns

Based on use of anti-VEGF agents, eyes were classified into three groups by the treatments provided over 2 years: group A was eyes only treated with anti-VEGF agents (anti-VEGF monotherapy), group B was eyes treated with anti-VEGF agents and other methods (combination therapy), and group C was eyes not treated with anti-VEGF agents. The visual and anatomical prognosis were assessed in each group and were compared among the groups.

Statistical analysis

Results are presented as the mean±SD or median with IQR. One-way analysis of variance was used to compare normally distributed continuous variables, while the Kruskal-Wallis H-test was employed to evaluate skewed variables. The χ^2 test was used to compare nominal scale variables. Treatment period comparisons were carried out with the paired t-test. A two-tailed p value <0.05 was considered to indicate statistical significance. Analyses were performed with SAS V.9.4 TS1M5 (SAS Institute, Cary, North Carolina, USA) and were carried out by an independent biostatistics data centre (STATZ Institute, Tokyo, Japan).

RESULTS

At the time of analysis, there were 2166 eyes in the STREAT-DME database. Based on the inclusion criteria, 2049 treatment-naïve eyes of 1552 patients with center-involving DME were eligible for this study. Patient characteristics are listed in table 1.

In this database, systemic conditions were assessed at the time of initial intervention for each eye. Thus, if an eligible patient had bilateral DME, systemic conditions at the time of initial intervention would be extracted separately for each eye. However, this study did not assess the relationship between clinical parameters and systemic conditions, so all 2049 eyes (497 bilateral and 1055 unilateral) were analysed.

For all eyes, baseline BCVA was 0.44±0.37 logMAR and final BCVA improved significantly to 0.40±0.42 logMAR (p<0.001) (table 2). The mean improvement was −0.04±0.40 logMAR, corresponding to 2.0 letters according to the ETDRS score. Baseline CMT was 443.8±154.8 μm and it showed a significant decrease to 335.6±154.8 μm (p<0.001) with the improvement of CMT being −108.2±186.8 μm.

Table 1 Patient demographics at initial treatment

	Overall	Anti-VEGF monotherapy	Combination therapy	Unused therapy	P value
Number of eyes	2049	427	807	815	–
Number of patients	1552	292	617	643	–
Mean age (years)	63.5±10.8	65.0±10.9	62.6±11.2	63.6±10.1	0.003
Sex, male/female	989/563	193/99	393/224	403/240	0.601
Duration of diabetes, (M)	94 (36–168)	85 (24–180)	72 (24–144)	120 (36–180)	0.063
HbA1c (%)	7.7±1.8	7.7±1.7	7.7±1.9	7.7±1.7	0.998
eGFR (mL/min/1.73 m^2)	64.8±27.2	66.1±28.2	66.6±27.3	62.4±26.6	0.102
Cataract surgery	n=818 (39.9%)	n=120 (28.1%)	n=389 (48.2%)	n=309 (37.9%)	<0.001
Peripheral photocoagulation	n=617 (30.1%)	n=72 (16.9%)	n=308 (38.2%)	n=237 (29.1%)	<0.001

eGFR, estimated glomerular filtration rate; HbA1c, glycohaemoglobin; VEGF, vascular endothelial growth factor.

Table 2 Visual and anatomical outcomes for 2 years

	Overall	Anti-VEGF monotherapy	Combination therapy	Unused therapy	P value
Baseline BCVA (logMAR)	0.44±0.37	0.45±0.35	0.48±0.36	0.40±0.38	<0.001
Good/Poor (eyes)	735/1314	144/283	243/564	348/467	<0.001
Final BCVA (logMAR)	0.40±0.42	0.37±0.42	0.46±0.40	0.35±0.44	<0.001
Good/Poor (eyes)	949/1100	211/216	314/493	424/391	<0.001
Difference of BCVA	−0.04±0.40	−0.09±0.39	−0.02±0.40	−0.05±0.39	0.012
P value	<0.001	<0.001	0.2253	0.0002	–
95% CI (logMAR)	−0.0622 to −0.0278	−0.1244 to −0.0494	−0.0450 to 0.0106	−0.0774 to −0.0237	
Baseline CMT (μm)	443.8±154.8	446.4±144.1	472.8±160.1	413.7±149.2	<0.001
Final CMT (μm)	335.6±139.6	329.0±126.5	348.6±151.1	326.2±133.5	0.003
Difference of CMT (μm)	−108.2±186.8	−117.4±174.1	−124.2±197.2	−87.5±180.8	<0.001
P value	<0.001	<0.001	<0.001	<0.001	–
95% CI (μm)	−116.3 to −100.0	−134.0 to −100.7	− 137.9 to −110.4	−100.0 to −74.9	

BCVA, best-corrected visual acuity; CMT, central macular thickness; VEGF, vascular endothelial growth factor.

A total of 451 eyes (22.0%) were 'improved', while 289 eyes (14.1%) became 'worsened' (figure 1, black bars). In 949 eyes (46.3%), final BCVA was better than 20/40 (figure 2, black bar).

As shown in table 3, 1234 eyes (60.2%) received anti-VEGF agents during the 2-year period and the mean number of doses was 3.8±3.3. In addition, 1077 (52.6%) eyes received local TA 2.0±1.3 times, 746 eyes (36.4%) received macular photocoagulation 1.9±1.4 times and 597 (29.1%) eyes received vitrectomy 1.1 ±0.3 times.

Two-year visual and anatomical prognosis according to treatment pattern

Among the 2049 treatment-naïve DME eyes, 427 eyes (20.9%) only received anti-VEGF therapy (group A), 806 eyes (39.2%) received anti-VEGF therapy combined with other therapies (local TA, macular photocoagulation and/or vitrectomy) (group B) and the other 815 eyes (39.8%) did not receive treatment with anti-VEGF agents (group C). The demographic profiles of each group showed no significant differences, except for mean age (table 1).

In group A (427 eyes), baseline BCVA was 0.45±0.35 and it improved significantly to 0.37±0.42 (p<0.001). Baseline CMT was 446.4±144.1 μm and it decreased significantly to 329.0 ±126.5 μm (p<0.001). Improvement of BCVA was −0.09 ±0.39, which converts to a gain of 4.5 letters (table 2). In this group, 105 eyes (24.6%) 'improved', and 51 eyes (11.9%) became 'worsened' (figure 1, white bars), while final BCVA was better than 20/40 in 211 eyes (49.4%) (figure 2, white bar). All 427 eyes received anti-VEGF agents, with a mean of 4.3±3.6 injections over 2 years. In brief, 191 eyes received IVB 2.0±1.4 times, 224 eyes received IVR 3.7±3.0 times and 138 eyes received IVA 4.7±3.3 times (table 3).

In group B (806 eyes), baseline BCVA was 0.48±0.36 and there was no significant change, with final BCVA being 0.46±0.40 (p=0.2253). However, CMT decreased significantly from 472.8±160.1 μm to 348.6±151.1 μm (p<0.001). Improvement of BCVA was −0.02±0.40, corresponding to a gain of 1 letter (table 2). In this group, 188 eyes (23.3%) 'improved' and 141 eyes (17.5%) became 'worsened' (figure 1, light-grey bars), with final BCVA being better than 20/40 in 314 eyes (38.9%) (figure 2, light-grey bar). All 806 eyes received anti-VEGF agents, with a mean of 3.6±3.1 injections over 2 years. In brief, 444 eyes received IVB 2.4±2.2 times, 354 eyes received IVR 3.1±2.6 times and 198 eyes received IVA 3.7±2.8 times. As other treatments, 524 eyes (64.9%) received local TA therapy (2.1±1.4 injections over 2 years, including 101 eyes given IVTA 1.8±1.2 times and 458 eyes given STTA 2.0±1.3 times), 361 eyes (44.7%) received macular photocoagulation and 295 eyes (36.6%) received vitrectomy (table 3).

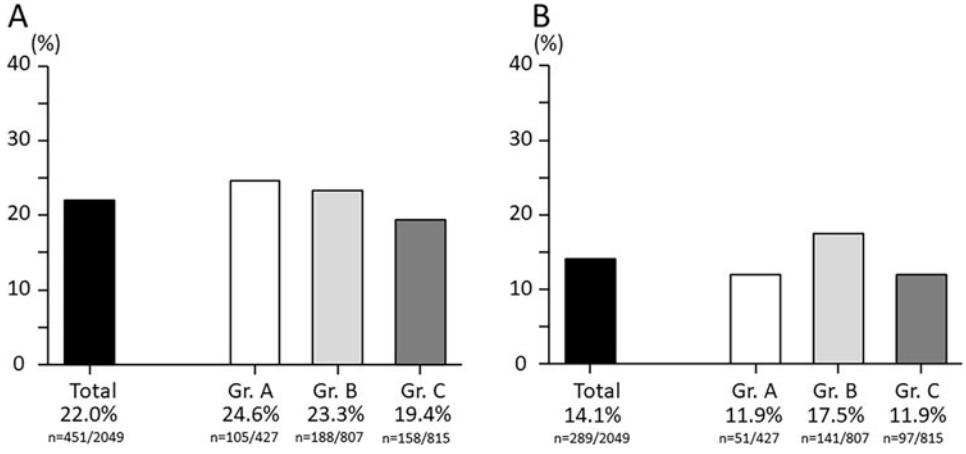

Figure 1 (A) Percentage of eyes with improvement by >15 letters from baseline. (B) Percentage of eyes with deterioration by >15 letters from baseline. Each graph shows all eyes (black bar), eyes given anti-vascular endothelial growth factor (VEGF) monotherapy (white bar), eyes given combination therapy (light-grey bar) and eyes not treated with anti-VEGF agents (dark-grey bar). Adapted from Shimura *et al*.[24]

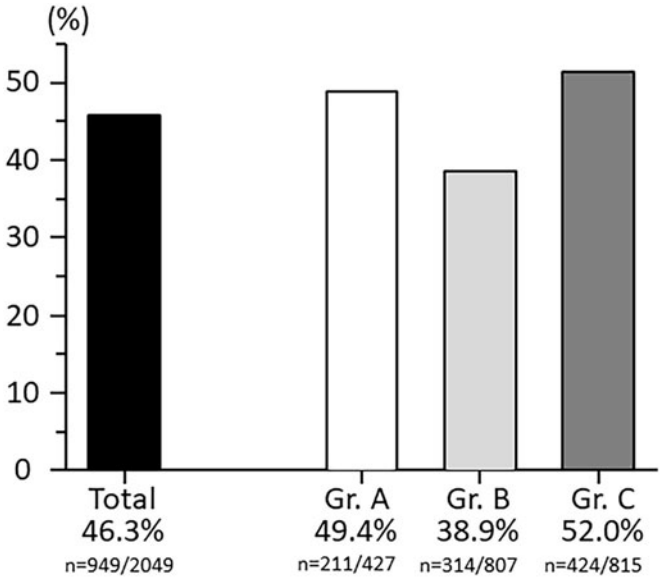

Figure 2 Percentage of eyes with 'good' final best-corrected visual acuity >20/40 (%). All eyes (black bar), eyes given anti-vascular endothelial growth factor (VEGF) monotherapy (white bar), eyes given combination therapy (light-grey bar) and eyes not treated with anti-VEGF agents (dark-grey bar). Adapted from Shimura *et al*.[24]

In group C (815 eyes), baseline BCVA was 0.40±0.38 and it improved significantly to 0.35±0.44 (p<0.001), while CMT decreased significantly from 413.7±149.2 μm to 326.2±133.5 μm (p<0.001). Improvement of BCVA was −0.05±0.39, corresponding to a gain of 2.5 letters. (table 2). In this group, 158 eyes (19.4%) 'improved' and 97 eyes (11.9%) became 'worsened' (figure 1, dark-grey bars), with final BCVA being better than 20/40 in 424 eyes (52.0%) (figure 2, dark-grey bar). All eyes received treatment other than anti-VEGF agents. In brief, 553 eyes (67.9%) received local TA therapy (1.9±1.2 injections) over 2 years, including 61 eyes given IVTA 1.7±1.0 times and 508 eyes given STTA 1.9±1.2 times, 385 eyes (47.2%) received macular photocoagulation and 302 eyes (37.1%) received vitrectomy (table 3).

Improvement of BCVA showed a significant difference among the groups, being worse in group B than group A (p=0.020). Baseline BCVA was significantly better in group C than in the other groups (p<0.001), while final BCVA was significantly worse in group B than in the other groups (p<0.001).

Baseline CMT was significantly different among the groups (group B>A>C: p<0.001), and final CMT was significantly greater in group B (p=0.006). Regression of CMT was significantly smaller in group C than in the other groups (p<0.001).

The percentage of eyes undergoing cataract surgery or laser photocoagulation outside the macular region differed among the groups, being higher in group B and lower in group A (p<0.001).

Can retina specialists maintain or gain 'good' VA after a 2-year treatment period?

In this study, among all 2049 eyes, 735 eyes (35.9%) had 'good' VA at baseline and 72.8% of them (535 eyes) still had 'good' VA at final assessment (figure 3A black bars), while 1314 eyes (64.1%) had 'poor' baseline VA (worse than 20/40) and 31.5% of them (414 eyes) improved to 'good' final VA (figure 3B, black bars). Thus, 949 (535+414) eyes (46.3%) had 'good' final VA of better than 20/40 (figure 2, black bar).

In group A, 33.7% of eyes had 'good' baseline VA and 75.0% of them maintained 'good' final VA, while 66.3% of eyes had 'poor' baseline VA and 36.4% of them improved to 'good' final VA (figure 3B, white bars). Thus, 49.4% of eyes had 'good' final VA in group A (figure 2, white bar).

In group B, 30.1% of eyeshad 'good' baseline VA and 63.4% of them maintained 'good' final VA, while 69.9% of eyes had 'poor' baseline VA and 28.4% of them improved to 'good' final VA (figure 3, light-grey bars). Thus, 38.9% of eyes had 'good' final VA in group B (figure 2, light-grey bar).

In group C, 42.7% of eyes had 'good' baseline VA and 78.4% of them maintained 'good' final VA, while 57.3% of eyes had

Table 3 Treatment frequency and its number of eyes

	Overall	Anti-VEGF monotherapy	Combination therapy	Unused therapy
Anti-VEGF	n=1234 (60.2%)	n=427 (100.0%)	n=807 (100.0%)	–
Number of times	3.8±3.3	4.3±3.6	3.6±3.1	–
Bevacizumab	n=635 (31.0%)	n=191 (44.7%)	n=444 (55.0%)	–
Number of times	2.2±2.0	2.0±1.4	2.4±2.2	–
Ranibizumab	n=578 (28.2%)	n=224 (52.5%)	n=354 (43.9%)	–
Number of times	3.3±2.8	3.7±3.0	3.1±2.6	–
Aflibercept	n=336 (16.4%)	n=138 (32.3%)	n=198 (24.5%)	–
Number of times	4.1±3.0	4.7±3.3	3.7±2.8	–
Corticosteroid	n=1077 (52.6%)	–	n=524 (64.9%)	n=553 (67.9%)
Number of times	2.0±1.3	–	2.1±1.4	1.9±1.2
Intravitreal TA	n=162 (7.9%)	–	n=101 (12.5%)	n=61 (7.5%)
Number of times	1.7±1.1	–	1.8±1.2	1.7±1.0
Subtenon TA	n=966 (47.1%)	–	n=458 (56.8%)	n=508 (62.3%)
Number of times	2.0±1.3	–	2.0±1.3	1.9±1.2
Macular photocoagulation	n=746 (36.4%)	–	n=361 (44.7%)	n=385 (47.2%)
Number of times	1.9±1.4	–	1.8±1.4	1.9±1.3
Vitrectomy	n=597 (29.1%)	–	n=295 (36.6%)	n=302 (37.1%)
Number of times	1.1±0.3	–	1.1±0.3	1.0±0.2

TA, triamcinolone acetonide; VEGF, vascular endothelial growth factor.

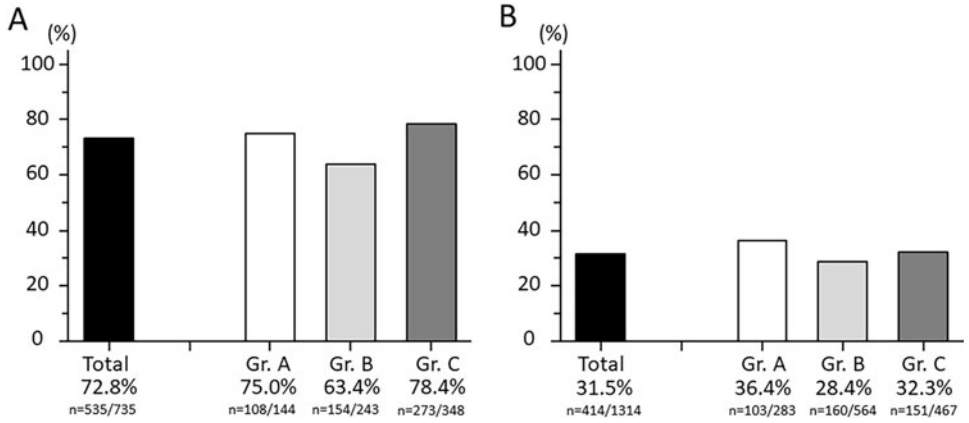

Figure 3 (A) Percentage of eyes with both 'good' final best-corrected visual acuity (BCVA) >20/40 and 'good' baseline BCVA >20/40. (B) Percentage of eyes improving to 'good' final BCVA >20/40 from 'poor' baseline BCVA <20/40. Each graph shows all eyes (black bar), eyes given anti-vascular endothelial growth factor (VEGF) monotherapy (white bar), eyes given combination therapy (light-grey bar) and eyes not treated with anti-VEGF agents (dark-grey bar). Adapted from Shimura *et al*.[24]

'poor' baseline VA and 32.3% of them improved to 'good' final VA (figure 3, dark-grey bars). Thus, 52.0% of eyes had 'good' final VA in group C (figure 2 dark-grey bar).

DISCUSSION

In this investigation of real-world outcomes for center-involving DME, treatment-naïve eyes showed a mean gain of 2 letters, 22.0% of eyes gained >15 letters and 46.3% of eyes maintained a final BCVA better than 20/40, but BCVA declined by >15 letters in 14.1% of eyes. These results were obtained after 2 years of treatment by retina specialists in Japan using 'order-made' protocols.

Of course, this study had several limitations by its retrospective nature. Treatment was selected by each physician, and only eyes observed for 2 years were assessed, so eyes with prompt recovery after brief intervention or eyes without improvement after multiple interventions may not have been followed for 2 years. In addition, this database did not contain enough information about systemic and ocular side effects during 2 years of intervention because some were recorded but the other were not in each clinical record. Although this limits the ability to assess the relationship between the 2-year prognosis and treatment (so p values are only nominal), this study revealed several pertinent insights. (1) Retina specialists in Japan did not always choose anti-VEGF agents for treatment of DME, and were less likely to use anti-VEGF agents for patients with a better baseline BCVA, (2) while anti-VEGF agents were used for patients with DME with a poor baseline BCVA and the visual prognosis was better if other therapies were not required. (3) In contrast, when anti-VEGF agents were used in combination with other therapies, it did not achieve adequate outcomes. (4) For ophthalmologists, the final goal of treating DME is to maintain socially useful BCVA exceeding 20/40, and retina specialists in Japan achieved this goal in only 46.3% of DME eyes.

Unlike previous real-world studies of DME treatment, this study was not limited to anti-VEGF therapy and was focused on the 2-year visual prognosis after any intervention for treatment-naïve DME. Previous studies focused on anti-VEGF therapy showed the following results after 2 years: +3.36 letters with 12.4~13.1 injections,[12] +3.0 letters with 8.6 injections[13] and +2.7 letters with 9.1 injections.[14] Other studies with a shorter duration have obtained results of +6.6 letters with 6.6 injections over 1 year[15] and +4.3~+4.9 letters with 2.6~3.8 injections over 6 months,[16] while a study with a longer duration showed an outcome of +6.6 letters with 7.7 injections over 4 years.[17] In our study, the visual prognosis of group A (+4.5 letters with 4.3 injections) was similar to the above results, but that of group B (+1.0 letter with 3.6 injections and additional interventions) was worse. Group B had worse baseline BCVA than the other groups, and may have included patients with DME that was resistant or insensitive to anti-VEGF agents.

Some previous clinical trials achieved a better 2-year visual prognosis with more injections of anti-VEGF agents including, +10~+12.8 letters with 15~16 injections,[18] +9.4~+11.5 letters with 13.5 injections,[19] +7~+9 letters with 10~12 injections[20] and +6.7~7.9 letters with 11.0~11.3 injections.[10]

It is not surprising that fewer anti-VEGF injections achieve a worse visual prognosis, because the clinical benefit of anti-VEGF therapy is limited to a duration of 4 weeks.[21 22] Accordingly, monthly treatment for DME will gain better results, both theoretically and actually. However, cost and compliance problems do not always allow continuous monthly injection of anti-VEGF agents, so both patients and retina specialists will seek other appropriate treatment options. In this study, group C showed improvement by +2.5 letters without use of anti-VEGF agents. In this group, mean baseline BCVA was 0.4 and was better than in the other two groups, so improvement of VA may have been limited by the 'ceiling effect'.[12] Although the possibility of a better visual prognosis being achieved if anti-VEGF agents had been used cannot be denied, 52.0% of the eyes in this group maintained a final BCVA better than 20/40 without anti-VEGF therapy, supporting the validity of this treatment option.

In both group B and group C, approximately 65% of eyes received local corticosteroid therapy, 45% received macular photocoagulation and 35% received vitrectomy. In previous real-world studies of anti-VEGF therapy for DME,[13] 65.9% of eyes received laser treatment, 14.1% received intravitreal dexamethasone and 8.2% received vitrectomy, while 59.4% of anti-VEGF non-responder eyes received intravitreal corticosteroids and 31.3% received vitrectomy, similar to our results for groups B and C. Considering that one-third of patients with DME have an incomplete response to anti-VEGF therapy,[11] the best option for second-line therapy always gives rise to debate. In Japan, retina specialists selected local corticosteroids as second-line therapy for approximately two-thirds of DME eyes, laser photocoagulation for half and vitrectomy for one-third. In this study, TA was administered by subtenon injection six times more frequently than by intravitreal injection. Intravitreal injection of TA has some adverse effects, including elevation of intraocular pressure, progression of cataract

and sterile endophthalmitis, while subtenon injection causes relatively few adverse effects[23] and can be combined with intravitreal injection of anti-VEGF agents to reduce the frequency of treatment.[24] Dexamethasone implants have not been approved in Japan, which is another reason why subtenon injection of TA was widely used by retina specialists. Although the efficacy of subtenon TA has not been investigated sufficiently, most retina specialists in Japan consider it as the best second-line option for DME. In the light of variable responses to anti-VEGF drugs, one needs to remember that DME is a heterogenous disease, and not everybody responds equally to these drugs, and there may be a genetic factor that determined the cytokine profile of each individual patient with DME. Thus the results are variable, and many patients poorly responsive to anti-VEGF drugs respond well to steroids.

Among previous studies of treatment for DME, baseline BCVA was limited to the range from 20/40 to 20/320 in the VIVID/VISTA study[25] and the RISE/RIDE study,[26] or from 20/32 to 20/160 in the RESTORE study.[27] In our real-world study, there was no limitation on baseline BCVA and it was positively correlated with final BCVA, as supported by previous results.[28] In our real-world setting, 68.0% of DME eyes with a baseline BCVA better than 20/40 also achieved a final BCVA better than 20/40, while only 31.5% eyes with a baseline BCVA worse than 20/40 improved to a final BCVA better than 20/40. Thus, intervention for DME should be started before BCVA deteriorates.

Although retrospective analysis of the STREAT-DME database does not provide accurate assessment of the prognosis and/or efficacy, the percentage of eyes maintaining socially useful VA after intervention can be determined. The clinical and social contribution of retina specialists can also be evaluated. In future, using this database, other studies analysing visual prognosis by starting year of treatment, or by baseline BCVA may bring interesting results. Or updating this database with longer period (5 years or more) of monitoring, it may also give more important information because most DME eyes have not been cured in 2 years.

Author affiliations
[1]Department of Ophthalmology, Tokyo Medical University Hachioji Medical Center, Hachioji, Japan
[2]Department of Ophthalmology, Diabetes Center, Tokyo Women's Medical University, Tokyo, Japan
[3]Department of Ophthalmology, Tokyo Medical University, Tokyo, Japan
[4]Department of Ophthalmology, School of Medical Sciences, University of Fukui, Yoshida, Japan
[5]Department of Ophthalmology and Visual Sciences, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan
[6]Department of Ophthalmology, Wakayama Medical University, Wakayama, Japan
[7]Department of Ophthalmology, St. Marianna University School of Medicine, Kawasaki, Japan
[8]Department of Ophthalmology, Tachikawa Hospital, Tachikawa, Japan
[9]Department of Ophthalmology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
[10]Department of Ophthalmology, Hachioji Medical Center, Tokyo Medical University, Tokyo, Japan
[11]Kyorin Eye Center, Kyorin University School of Medicine, Mitaka, Japan
[12]Department of Ophthalmology, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan
[13]Deparment of Ophthalmology, Shinshu University School of Medicine, Matsumoto, Japan
[14]Department of Ophthalmology, Hyogo College of Medicine, Nishinomiya, Japan
[15]Department of Ophthalmology, Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan
[16]Department of Ophthalmology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan
[17]Department of Ophthalmology, Sapporo City General Hospital, Sapporo, Japan
[18]Departmet of Ophthalmology, Yamaguchi University Graduate School of Medicine, Ube, Japan
[19]Department of Ophthalmology, Mie University Graduate School of Medicine, Tsu, Japan
[20]Department of Ophthalmology, Japanese Red Cross Otsu Hospital, Otsu, Japan
[21]Department of Ophthalmology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan
[22]Hikichi Eye Clinic, Sapporo, Japan
[23]Department of Ophthalmology, Showa General Hospital, Kodaira, Japan
[24]Department of Ophthalmology, National Defense Medical College, Tokorozawa, Japan
[25]Department of Ophthalmology, St. Luke's International Hospital, Tokyo, Japan
[26]Department of Ophthalmology, Nara Medical University Graduate School of Medicine, Kashihara, Japan
[27]Department of Ophthalmology, Kobe University Graduate School of Medicine, Kobe, Japan

Acknowledgements The authors would like to thank Katsunori Shimada, PhD working in STATZ Institute Inc. for providing statistical analysis.

Collaborators J-CREST (Japan Clinical Retina Study) group.

Contributors Contributions of the authors by data acquisition: Hidetaka Noma, Ryosuke Motohashi and Makoto Imazeki in Department of Ophthalmology, Tokyo Medical University, Hachioji Medical Center. Takuya Utsumi MD in Department of Ophthalmology, Tokyo Medical University. Eiko Tsuzuki MD in Department of Ophthalmology and Visual Sciences, Graduate School of Biomedical Sciences, Nagasaki University. Shizuya Saika MD in Department of Ophthalmology, Wakayama Medical University. Ryutaro Yamanishi MD in Department of Ophthalmology, National Tokyo Medical Center. Takao Kashiwagi MD and Fumi Gomi MD in Department of Ophthalmology, Hyogo College of Medicine. Takashi Katome MD in Department of Ophthalmology, Institute of Biomedical Sciences, Tokushima University Graduate School. Keiichi Nishikawa MD in Department of Ophthalmology, Japanese Red Cross Otsu Hospital. Mitsuru Nakazawa MD in Department of Ophthalmology, Hirosaki University Graduate School of Medicine. Masaru Takeuchi MD in Department of Ophthalmology, National Defense Medical College. Nahoko Ogata MD in Department of Ophthalmology, Nara Medical University.

Funding This study was supported by clinical research grant-in-aid by Tokyo Medical University. No conflicting relationship exists for any authors. This study is registered with the University Hospital Medical Information Network individual case data repository (UMIN#23160).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol was reviewed and approved by the Institutional Review Board of each participating centre, and the study was registered with the University Hospital Medical Information Network individual case data repository (UMIN#23160).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on request.

ORCID iDs
Masahiko Shimura http://orcid.org/0000-0001-5456-6374
Yoshinori Mitamura http://orcid.org/0000-0002-4813-672X
Kenji Yamashiro http://orcid.org/0000-0001-9354-8558

REFERENCES

1 Yau JWY, Rogers SL, Kawasaki R, *et al*. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;35:556–64.
2 Das A, McGuire PG, Rangasamy S. Diabetic macular edema: pathophysiology and novel therapeutic targets. *Ophthalmology* 2015;122:1375–94.
3 Barham R, El Rami H, Sun JK, *et al*. Evidence-Based treatment of diabetic macular edema. *Semin Ophthalmol* 2017;32:56–66.
4 Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for Diabetic Macular Edema, Report #1. *Arch Ophthalmol* 1985;103:1796–806.
5 Lewis H, Abrams GW, Blumenkranz MS, *et al*. Vitrectomy for diabetic macular traction and edema associated with posterior hyaloidal traction. *Ophthalmology* 1992;99:753–9.
6 Jonas JB, Kreissig I, Söfker A, *et al*. Intravitreal injection of triamcinolone for diffuse diabetic macular edema. *Arch Ophthalmol* 2003;121:57–61.
7 Verma LK, Vivek MB, Kumar A, *et al*. A prospective controlled trial to evaluate the adjunctive role of posterior subtenon triamcinolone in the treatment of diffuse diabetic macular edema. *J Ocul Pharmacol Ther* 2004;20:277–84.
8 Stewart MW. Anti-Vegf therapy for diabetic macular edema. *Curr Diab Rep* 2014;14:510.

9 Heier JS, Korobelnik J-F, Brown DM, *et al*. Intravitreal aflibercept for diabetic macular edema: 148-Week results from the VISTA and vivid studies. *Ophthalmology* 2016;123:2376–85.
10 Lang GE, Berta A, Eldem BM, *et al*. Two-year safety and efficacy of ranibizumab 0.5 mg in diabetic macular edema: interim analysis of the restore extension study. *Ophthalmology* 2013;120:2004–12.
11 Stewart MW. Treatment of diabetic retinopathy: recent advances and unresolved challenges. *World J Diabetes* 2016;7:333–41.
12 Ciulla TA, Bracha P, Pollack J, *et al*. Real-world outcomes of anti-vascular endothelial growth factor therapy in diabetic macular edema in the United States. *Ophthalmol Retina* 2018;2:1179–87.
13 Maggio E, Sartore M, Attanasio M, *et al*. Anti-vascular endothelial growth factor treatment for diabetic macular edema in a real-world clinical setting. *Am J Ophthalmol* 2018;195:209–22.
14 Hodzic-Hadzibegovic D, Sander BA, Monberg TJ, *et al*. Diabetic macular oedema treated with intravitreal anti-vascular endothelial growth factor - 2-4 years follow-up of visual acuity and retinal thickness in 566 patients following Danish national guidelines. *Acta Ophthalmol* 2018;96:267–78.
15 Patrao NV, Antao S, Egan C, *et al*. Real-world outcomes of ranibizumab treatment for diabetic macular edema in a United Kingdom National health service setting. *Am J Ophthalmol* 2016;172:51–7.
16 Koç İrem, Kadayıfçılar S, Eldem B. Real-World results of intravitreal ranibizumab, bevacizumab, or triamcinolone for diabetic macular edema. *Ophthalmologica* 2018;239:85–93.
17 Epstein D, Amrén U. Long-Time outcome in patients treated with ranibizumab for diabetic macular edema: a 4-year study. *Retina* 2018;38:183–6.
18 Wells JA, Glassman AR, Ayala AR, *et al*. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology* 2016;123:1351–9.
19 Brown DM, Schmidt-Erfurth U, Do DV, *et al*. Intravitreal aflibercept for diabetic macular edema: 100-Week results from the VISTA and vivid studies. *Ophthalmology* 2015;122:2044–52.
20 Elman MJ, Bressler NM, Qin H, *et al*. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2011;118:609–14.
21 Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF trap. *Br J Ophthalmol* 2008;92:667–8.
22 Stewart MW, Rosenfeld PJ, Penha FM, *et al*. Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor Trap-eye). *Retina* 2012;32:434–57.
23 Ogura Y, Shimura M, Iida T, *et al*. Phase II/III clinical trial of Sub-Tenon injection of triamcinolone acetonide (WP-0508ST) for diabetic macular edema. *Ophthalmologica* 2019;241:161–9.
24 Shimura M, Yasuda K, Minezaki T, *et al*. Reduction in the frequency of intravitreal bevacizumab administrations achieved by posterior subtenon injection of triamcinolone acetonide in patients with diffuse diabetic macular edema. *Jpn J Ophthalmol* 2016;60:401–7.
25 Korobelnik J-F, Do DV, Schmidt-Erfurth U, *et al*. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology* 2014;121:2247–54.
26 Brown DM, Nguyen QD, Marcus DM, *et al*. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: rise and ride. *Ophthalmology* 2013;120:2013–22.
27 Mitchell P, Bandello F, Schmidt-Erfurth U, *et al*. The restore study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011;118:615–25.
28 Sophie R, Lu N, Campochiaro PA. Predictors of functional and anatomic outcomes in patients with diabetic macular edema treated with ranibizumab. *Ophthalmology* 2015;122:1395–401.