JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Treatment of diabetic macular edema in real-world clinical practice: The effect of aging

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

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

Keywords
Aging, Diabetes, Diabetic macular edema

***Correspondence**
Sentaro Kusuhara
Tel.: +81-78-382-6048
Fax: +81-78-382-6059
E-mail address:
kusu@med.kobe-u.ac.jp

J Diabetes Investig 2022; 13: 1339–1346

doi: 10.1111/jdi.13801

ABSTRACT

Aims/Introduction: In older patients, the management of diabetic macular edema (DME) can be complicated by comorbidities, geriatric syndrome, and socioeconomic status. This study aims to evaluate the effects of aging on the management of DME.

Materials and Methods: This is a real-world clinical study including 1,552 patients with treatment-naïve center-involved DME. The patients were categorized into 4 categories by age at baseline (C1, <55; C2, 55–64; C3, 65–74; and C4, ≥75 years). The outcomes were the change in logarithm of the minimum angle of resolution best-corrected visual acuity (logMAR BCVA) and central retinal thickness (CRT), and the number of treatments from baseline to 2 years.

Results: From baseline to 2 years, the mean changes in logMAR BCVA from baseline to 2 years were −0.01 in C1, −0.06 in C2, −0.07 in C3, and 0.01 in C4 ($P = 0.016$), and the mean changes in CRT were −136.2 μm in C1, −108.8 μm in C2, −100.6 μm in C3, and −89.5 μm in C4 ($P = 0.008$). Treatments applied in the 2 year period exhibited decreasing trends with increasing age category on the number of intravitreal injections of anti-VEGF agents ($P = 0.06$), selecting local corticosteroid injection ($P = 0.031$), vitrectomy ($P < 0.001$), and laser photocoagulation outside the great vascular arcade ($P < 0.001$).

Conclusions: Compared with younger patients with DME, patients with DME aged ≥75 years showed less frequent treatment, a lower BCVA gain, and a smaller CRT decrease. The management and visual outcome in older patients with DME would be unsatisfactory in real-world clinical practice.

Received 30 December 2021; revised 8 March 2022; accepted 5 April 2022

INTRODUCTION

According to a report from the United Nations, approximately 700 million persons worldwide were aged ≥65 years in 2019, and the percentage of the population aged ≥65 years was estimated to increase from 9.1% in 2019 to 16.7% in 2050[1]. Together with the fact that older adults are at high risk for the development of diabetes and that the life expectancy of the population is increasing[2], the number of older adults with diabetes is expected to grow markedly. Preserving life-long vision is one of the pivotal goals of diabetes treatment because both aging and diabetes are recognized as risk factors for vision loss. Indeed, in a cross-sectional population-based study, older age, type 2 diabetes, and memory problems were identified as factors associated with visual impairment[3]. Conversely, in the Diabetes and Aging Study, a cohort study including 72,310 patients aged ≥60 years with type 2 diabetes, the rate of diabetic eye disease increased with age when the duration of diabetes was less than 10 years, but it was greatest in the youngest (60–69 years) age group in the analysis of subjects with a ≥10 years duration of diabetes[4]. Like this discrepancy, the complex and heterogeneous health status exhibited by older adults could considerably affect treatment outcomes in diabetic eye disease. However, as most previous observational and interventional clinical studies did not focus on aging, there are no evidence-based management guidelines on diabetic ocular disorders in older adults.

Diabetic macular edema (DME) is a leading cause of severe visual impairment in patients with diabetes. The current standard of care for DME is intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents, since randomized clinical trials (RCTs) proved its efficacy and safety[5–8]. However, to truly benefit from anti-VEGF therapy, patients with DME require long-term regular injection of costly anti-VEGF agents. Moreover, roughly one-third of patients show an incomplete response to anti-VEGF therapy[9]. Therefore, these problems might make this treatment strategy untenable for most patients with diabetes in the real-world[10–16]. In older patients, the management of DME would be further complicated by comorbidities, geriatric syndrome, and socioeconomic status[17,18] and thus it should be prioritized and modified to meet the patient's individual goal, which stems from various personal values and preferences for treatment.

Ideally, RCTs are needed to obtain corroborative evidence on the optimal management of DME in older adults. However, to the best of our knowledge, no RCTs that focus on the treatment of aged patients with DME have been conducted so far, probably because of the comorbidities and geriatric problems frequently observed in this population. It may sound plausible that the second-best choice is to extrapolate the results of previous RCTs to older groups or to conduct secondary analysis of the data of previous RCTs, but caution must be exercised as most RCTs enrolled an insufficient number of aged people and restricted some interventions commonly selected in clinical practice[5–8]. Accordingly, a large-scale retrospective study would be an optimal solution to this problem.

In this study, we utilized and analyzed the clinical data of more than 1,500 patients with treatment-naïve DME, aiming to provide novel information on the current status of medical care for older patients with DME in real-world clinical settings in Japan. Because no similar studies have been conducted so far, the data presented in this study would greatly help to improve the management of DME in an older population.

MATERIALS AND METHODS

Study design

This was a secondary analysis of a large-scale multicenter retrospective study of Survey of Treatment for DME (STREAT-DME) study conducted by the Japan Clinical Retina Study (J-CREST) group[16,19]. The STREAT-DME study conformed to the tenets of the Declaration of Helsinki, and institutional review board approval was granted at each institution. The data of the STREAT-DME study was registered at University Hospital Medical Information Network (UMIN) Clinical Trial (https://www.umin.ac.jp/english/) (UMIN#23160) accredited by the International Committee of Medical Journal Editors.

The STREAT-DME study database contains anonymous clinical data of 1,552 patients with treatment-naïve center-involved DME who were treated for the first time between January 2010 and December 2015 and followed for at least 2 years in a real-world clinical setting at 27 sites in Japan. The following data were extracted from the STREAT-DME study database: age, sex, eye laterality, duration of diabetes, serum HbA1c and creatinine levels, and estimated glomerular filtration rate (eGFR), year, decimal best-corrected visual acuity (BCVA), and central retinal thickness (CRT) measured by optical coherence tomography at the start of treatment (defined as baseline), number and type of treatment at 2 years, and BCVA and CRT at 2 years. Decimal BCVA data were converted to the logarithm of minimum angle of resolution (logMAR) BCVA values as needed.

A diagnosis of center-involved DME was made by an ophthalmologist at each site, and there were no restrictions regarding the treatment of DME, which included intravitreal injection of anti-VEGF agents (1.25 mg/0.05 mL of bevacizumab [IVB], 0.5 mg/0.05 mL of ranibizumab [IVR], or 2.0 mg/0.05 mL of aflibercept [IVA]), local corticosteroid injection (intravitreal injection of 4 mg/0.1 mL of triamcinolone acetonide [IVTA] or posterior sub-Tenon's injection of 20 mg/0.5 mL of triamcinolone acetonide [STTA]), focal/grid laser photocoagulation to the macula (focal/grid PC), and pars plana vitrectomy (PPV). Cataract surgery or laser photocoagulation outside the great vascular arcade (outside PC) at the 2 year period was also considered because both might affect BCVA and/or CRT.

Outcome measures

To compare the effect of aging, the subjects were divided into 4 categories (C1, <55 years; C2, 55–64 years; C3, 65–74 years; and C4, ≥75 years) based on the age at baseline. The primary outcome was defined as the change in logMAR BCVA from baseline to 2 years after initial treatment. The secondary outcomes were changed in the proportion of logMAR BCVA category (>1.0, >0.3 and ≤1.0, ≤0.3) at 2 years from baseline, change in the proportion of BCVA improvement category defined as the degree of logMAR BCVA difference ('improved' [≤−0.3], 'unchanged' [−0.3 < and <0.3], and 'worsened' [≥0.3]) from baseline to 2 years, the change in CRT from baseline to 2 years, and the number of treatment and the percentage of treated eye in each treatment at the 2 year period.

Statistical analyses

We applied linear regression analysis to compare continuous variables among age categories. The Cochran–Armitage test for trend was used to test for a linear trend in ordered categorical variables, and the Cochran–Mantel–Haenszel test was employed to compare correlated categorical data. To compare changes at 2 years from baseline, paired *t*-test and Wilcoxon signed-rank test were used as appropriate. A two-tailed *P*-value <0.05 was considered statistically significant. SAS software version 9.4 TS1M7 (SAS Institute, Cary, NC, USA) was used for analyses, and all analyses were conducted by an independent biostatistics data center (STATZ Institute, Tokyo, Japan).

RESULTS

The STREAT-DME database contained data of 2049 eyes from 1,552 patients with treatment-naïve center-involved DME, but one patient with unilateral DME was excluded because of uncertain information on age. Accordingly, data on the remaining 2048 eyes from 1,551 patients were analyzed. Baseline characteristics according to age category are summarized in Table 1. The mean age of patients was 63.5 years, with 13.1% of the population aged ≥75 years. There were several significant differences in age categories: a decreasing trend of male predominance and serum HbA1c and eGFR levels and an increasing trend of the duration of diabetes as age category advances. BCVA tended to decline with advancing age category shown by a decreasing trend of median decimal BCVA and an increasing trend of mean logMAR BCVA.

Visual outcomes

The mean (standard deviation [SD]) logMAR BCVAs were 0.38 (0.35) in C1 (<55 years), 0.43 (0.37) in C2 (55–64 years), 0.45 (0.36) in C3 (65–74 years), and 0.53 (0.39) in C4 (≥75 years) at baseline and 0.37 (0.53) in C1, 0.37 (0.42) in C2, 0.38 (0.37) in C3, and 0.54 (0.40) in C4 at 2 years. There was a small but significant improvement in BCVA at 2 years in C2 and C3 ($P < 0.001$ each). However, BCVA in C1 and C4 did not show a significant change after the 2 year treatment ($P = 0.635$ and $P = 0.645$, respectively) (Figure 1). The mean (SD) changes in logMAR BCVA at 2 years from baseline were −0.01 (0.53) in C1, −0.06 (0.39) in C2, −0.07 (0.34) in C3, and 0.01 (0.35) in C4 ($P = 0.016$). Changes in the proportion of logMAR BCVA category (>1.0, >0.3 and ≤1.0, ≤0.3) at 2 years from baseline showed similar results. The percentages of eyes with logMAR BCVA >1.0/>0.3 and ≤1.0/≤0.3 were 6/48/46% in C1, 6/58/36% in C2, 6/60/34% in C3, and 8/65/27% in C4 at baseline and 7/40/53% in C1, 4/49/47% in C2, 6/46/48% in C3, and 12/59/29% in C4 at 2 years. C2 and C3 exhibited a significantly increased proportion of better BCVA ($P < 0.001$ each), while C1 and C4 did not ($P = 0.199$ and $P = 0.914$, respectively) (Figure S1). The change in the proportion of BCVA improvement category from baseline to 2 years reached statistical significance among the age categories ($P = 0.012$). The percentages of eyes with 'improved' BCVA were 22% in C1, 24% in C2, 23% in C3, and 14% in C4; those of eyes with 'unchanged' BCVA were 62% in C1, 64% in C2, 63% in C3, and 64% in C4; and those of eyes with 'worsened' BCVA were 16% in C1, 12% in C2, 14% in C3, and 18% in C4 (Figure S2).

Table 1 | Baseline characteristics by age categories

Variable	C1 (<55 years)	C2 (55–64 years)	C3 (65–74 years)	C4 (≥75 years)	*P* value
Number of eyes	363	649	778	258	NA
Number of patients	271	482	595	203	NA
Age, mean (SD), years	46.5 (6.7)	60.2 (2.7)	69.1 (2.9)	78.9 (3.5)	<0.001†
Sex, No. (%), female	67 (25)	178 (37)	220 (37)	98 (48)	<0.001‡
Eye, No. (%), right	178 (49)	310 (48)	374 (48)	115 (45)	0.974‡
Duration of diabetes, mean (SD), months	85.9 (74.2)	101.6 (103.9)	136.0 (118.7)	172.0 (135.0)	<0.001†
HbA1c, mean (SD), %	8.3 (2.2)	7.7 (1.8)	7.5 (1.5)	7.3 (1.4)	<0.001†
eGFR, mean (SD), mL/min/1.73m^2	71.4 (34.9)	65.9 (26.1)	61.3 (24.0)	60.0 (20.6)	<0.001†
Decimal BCVA, median (interquartile range)	0.5 (0.3–0.7)	0.4 (0.2–0.7)	0.4 (0.2–0.6)	0.4 (0.2–0.6)	<0.001§
logMAR BCVA, mean (SD)	0.38 (0.35)	0.43 (0.37)	0.45 (0.36)	0.53 (0.39)	<0.001†
Central retinal thickness, mean (SD), μm	454.8 (170.6)	442.3 (144.1)	440.1 (156.3)	443.0 (153.0)	0.268†

BCVA, best-corrected visual acuity; eGFR, estimated glomerular filtration rate; logMAR, logarithm of minimum angle of resolution; NA, not applicable; SD, standard deviation. †Linear regression analysis; ‡Cochran-Armitage test for trend; §Cochran–Mantel–Haenszel test.

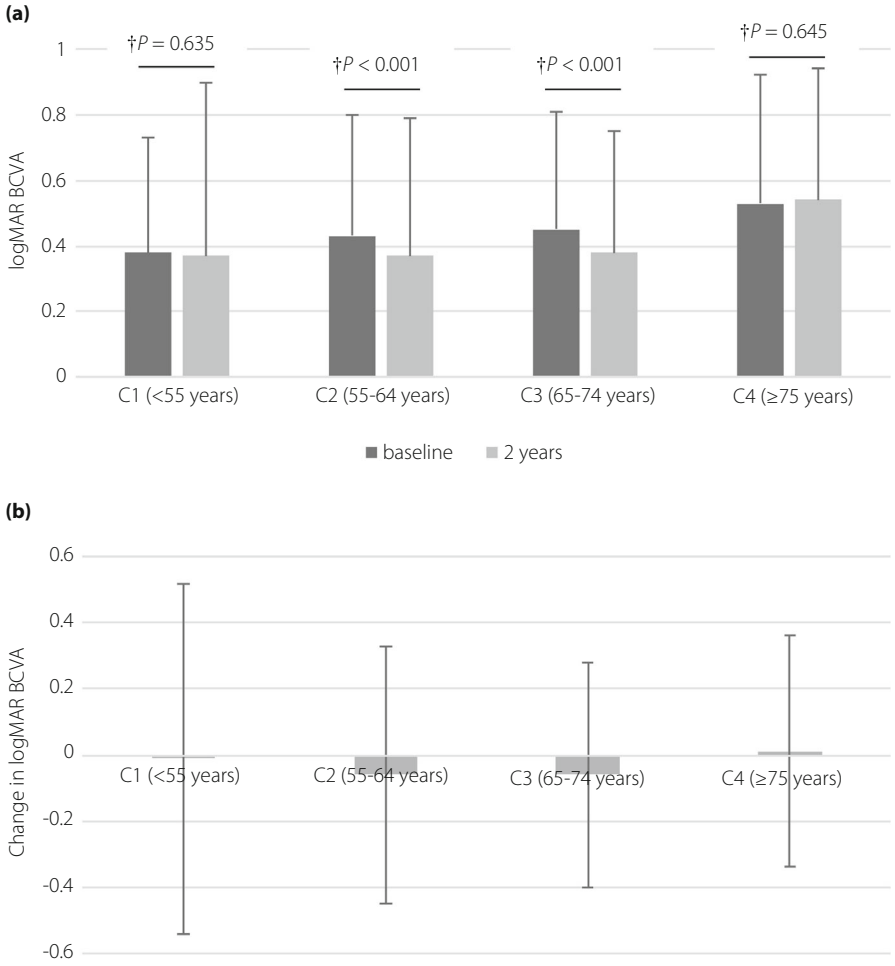

Figure 1 | Best-corrected visual acuity at baseline and 2 years in each age category. logMAR BCVA, logarithm of minimum angle of resolution best-corrected visual acuity. Error bar, standard deviation. †Paired *t*-test.

Anatomical outcomes

The mean (SD) CRTs were 454.8 (170.6) μm in C1, 442.3 (144.1) μm in C2, 440.1 (156.3) μm in C3, and 443.0 (153.0) μm in C4 at baseline ($P = 0.516$) and 318.6 (126.3) μm in C1, 333.5 (137.2) μm in C2, 339.5 (135.3) μm in C3, and 353.5 (171.1) μm in C4 at 2 years ($P = 0.017$). The CRT significantly decreased from baseline at 2 years in each age category ($P < 0.001$ each). The mean (SD) changes in CRT were −136.2 (192.8) μm in C1, −108.8 (180.6) μm in C2, −100.6 (188.7) μm in C3, and −89.5 (184.4) μm in C4 ($P = 0.008$) (Figure 2).

Selected treatments

The treatments applied at the 2 year period are shown in Table 2. As the patients were treated in the real-world, various types of treatments had been applied to one patient. A significant decreasing trend with advancing age category was observed on local corticosteroid injection, PPV, and outside PC, and intravitreal injection of anti-VEGF agents and focal/grid PC showed no significant trend. However, the mean (SD) number of intravitreal injections of anti-VEGF agents was 4.0 (3.5) in C1, 3.9 (3.1) in C2, 4.0 (3.5) in C3, and 3.1 (2.7) in C4 ($P = 0.060$), showing that patients aged ≥75 years were less frequently treated with anti-VEGF agents. Conversely, the frequency of laser photocoagulation to the macula did not show this predisposition. The mean (SD) number of focal/grid PC was 1.8 (1.2) in C1, 1.9 (1.4) in C2, 1.9 (1.4) in C3, and 1.6 (1.1) in C4 ($P = 0.685$).

DISCUSSION

In the current study, the analyses of baseline characteristics in our study disclosed age-related differences in some variables. While 75% of patients were male in the age category of <55 years, the percentage gradually decreased with age to approximately 50% in the age category of ≥75 years. This loss of male predominance in the prevalence rate with advancing age in our cohort was consistent with those of a previous

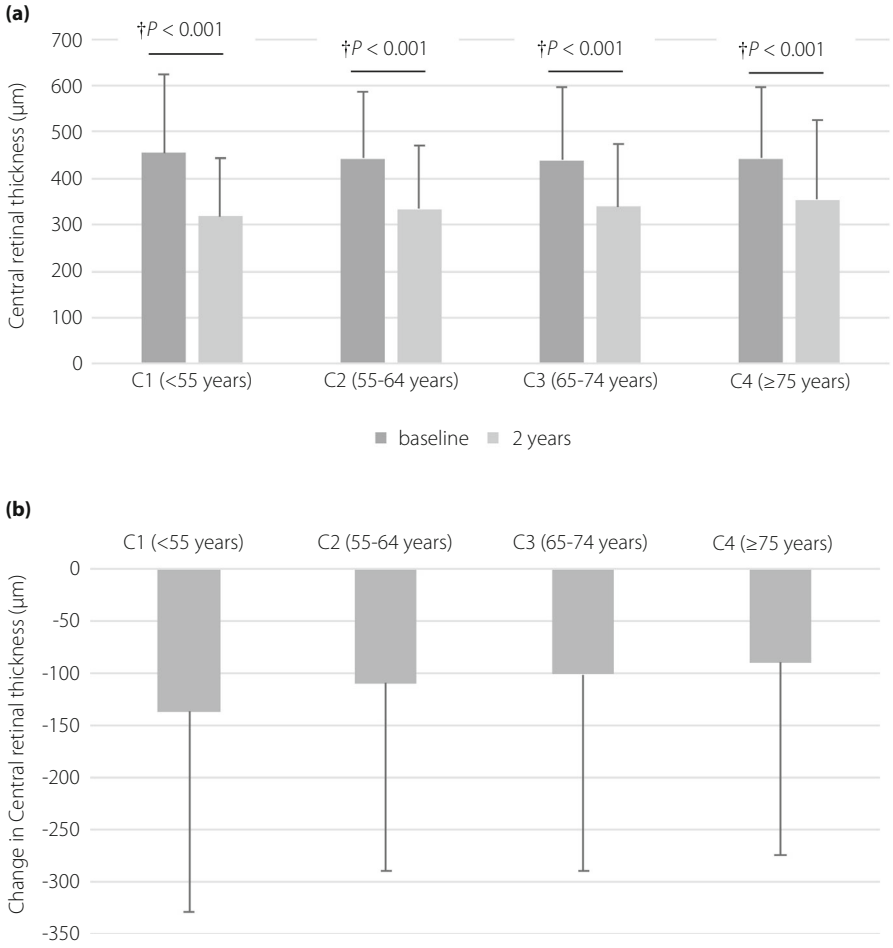

Figure 2 | Central retinal thickness at baseline and 2 years in each age category. †Paired *t*-test.

Table 2 | Treatments applied during 2 year period

Variable	C1 (<55 years)	C2 (55–64 years)	C3 (65–74 years)	C4 (≥75 years)	*P* value†
Intravitreal injection of anti-VEGF agents	232 (63.9)	379 (58.4)	457 (58.7)	166 (64.3)	0.846
Bevacizumab	126 (34.7)	200 (30.8)	215 (27.6)	94 (36.4)	0.547
Ranibizumab	100 (27.5)	191 (29.4)	219 (28.1)	68 (26.4)	0.680
Aflibercept	64 (17.6)	95 (14.6)	138 (17.7)	39 (15.1)	0.962
Local corticosteroid injection	197 (54.3)	356 (54.9)	405 (52.1)	118 (45.7)	0.031
Intravitreal injection of TA	27 (7.4)	50 (7.7)	63 (8.1)	22 (8.5)	0.573
Posterior sub-Tenon's injection of TA	172 (47.4)	319 (49.2)	371 (47.7)	103 (39.9)	0.107
Photocoagulation					
Focal/grid PC	126 (34.7)	247 (38.1)	280 (36.0)	93 (36.0)	0.965
Outside PC	180 (49.6)	282 (43.5)	282 (36.2)	74 (28.7)	<0.001
Surgery					
Cataract surgery	102 (28.1)	229 (35.3)	224 (28.8)	62 (24.0)	0.072
Pars plana vitrectomy	111 (30.6)	230 (35.4)	210 (27.0)	46 (17.8)	<0.001

Data are provided as mean (standard deviation). †Cochran-Armitage test for trend. focal/grid PC, focal/grid laser photocoagulation to the macula; Outside PC, laser photocoagulation outside the great vascular arcade; TA, triamcinolone acetonide; VEGF, vascular endothelial growth factor.

study[20]. Although the reason is unknown, the difference in socioeconomic status and lifestyle and biology between men and women might have some impact on it. It is well known that the duration of diabetes increases with age, and that aging dramatically affects kidney function[2]. Our data showed the same trend. Regarding the decreasing trend of HbA1c level with advancing age category, one possible explanation is that older retired patients had more time to frequently visit clinics than younger working-age patients.

Concerning the visual outcome, significant BCVA gains (equivalent to 2–3 letters in the Early Treatment Diabetic Retinopathy Study [ETDRS] letter score) was observed after the 2 year treatment in age category C2 (55–64 years) and C3 (65–74 years), but no significant BCVA change was obtained in age category C1 (<55 years) or C4 (≥75 years). Obviously, the BCVA improvement values are far smaller than those reported in RCTs[5–8], consistent with the widely accepted idea that therapeutic outcomes in real-world studies tend to be inferior to those in RCTs. Therefore, worthy of attention here would be the difference in BCVA gains among age categories. In this study, patients aged ≥75 years showed mean BCVA loss of 0.5 ETDRS letters after the 2 year treatment. There might be common factors that affect visual outcome in older patients with DME because a subgroup analysis of RESTORE study, an RCT that aimed to demonstrate superiority of ranibizumab monotherapy alone or combined with laser over laser alone in DME, showed better mean BCVA gains (7.4 ETDRS letters) in younger subjects (<65 years) than that (4.4 ETDRS letters) in older subjects (≥65 years) 12 months after the intervention for DME[21]. Conversely, the reason that the patients aged <55 years had insufficient BCVA gains in our study was unknown, although a better baseline BCVA in the younger group could partially be accounted for by the ceiling effect. However, with the points discussed below, we speculated that it might be attributed to the severity of DR or poorer patient compliance or both. Pragmatic real-world studies confront a broader variety of, and more heterogenetic, problems in daily clinical practice than RCTs and reflect the overall trend of clinical goals and practice patterns in a disease management cohort[22]. In the STREAT-DME study cohort, preserving BCVA above a certain level might have been a primary goal in patients aged ≥75 years. In this age category, the percentages of eyes with logMAR BCVA ≤0.3 (Snellen BCVA ≥20/40) were 27% at baseline and 29% at 2 years. In addition, more than 80% of eyes in this age category showed unchanged or improved BCVA after the 2 year treatment. One conceivable explanation of these results is that the retina specialists compromised with the patients on DME management considering various geriatric conditions, which is common in the management of older adults with diabetes[17].

Abnormal thickening of the retina is an essential feature of DME, and therefore a change in retinal thickness has been used as an anatomical parameter to evaluate treatment response in eyes with DME. In the present study, the anatomical outcome measured by CRT demonstrated no significant difference among age categories at baseline. However, although a certain degree of CRT improvement was obtained in each age category, the overall mean CRT at 2 years (335.7 μm) was much higher than that in previous RCTs (<300 μm in most RCTs and <200 μm in the RIDE trial)[5–8], and a significant trend was observed that the mean decrement in CRT is lower with increasing age group. These results indicate that the patients in the STREAT-DME study cohort were undertreated (treated inadequately) like in other real-world clinical studies compared with those in RCTs where ideal intensive treatment had been done. The putative factors associated with this undertreatment are discussed below. In addition, Figures 1 and 2 clearly demonstrate the discrepancy between visual and anatomical outcomes observed in patients aged ≥75 years. Although its reasons should be explored in future studies, it might stem from ocular characteristics specific to older patients with DME such as severe ischemia and/or retinal degeneration at the macula.

It is well known that the treatment can chiefly affect both visual and anatomical outcomes in eyes with DME. From this point of view, the applied treatment in the 2 year period clearly showed differences among age categories. In brief, intravitreal injections of anti-VEGF agents, local corticosteroid injection, PPV, and outside PC were less frequently performed in advanced age category. The higher incidence of severe disease in younger patients or the social sentiment to avoid intensive treatment in older patients (e.g., increased risk of arterial thromboembolic events in older adults) might be a reason for that. Economic burden certainly modified the results. In Japan, the health insurance system that covers almost all residents allows easy access to treatment. With the system, patients only pay part of the total cost, and the copayment in patients aged <70 years, 71–74 years, and ≥ 75 years are set to be 30%, 20%, and 10%, respectively. Moreover, there are designated ceilings per month for personally borne medical expenses: 730 US dollars for aged <70 years and 110 US dollars for aged ≥70 years (please be notified that anti-VEGF therapy is relatively expensive in Japan because it potentially costs 110–450 US dollars every month). In fact, the percentages of local corticosteroid injection (14.1%) and PPV (8.2%) selected for the treatment of DME in a real-world study conducted in the United States were lower than that in our study[23], and the patients in other large-scale real-world studies were mostly treated with anti-VEGF monotherapy[11–15]. Taken together, patients and physicians might have collaborated with each other to find the best balance between risk/burden and visual/anatomical outcomes in the STREAT-DME study cohort. As this study aimed not to disclose the efficacy of a certain treatment but to obtain the overall picture (or to know the effectiveness) of the 2 year treatment outcomes in real-world clinical settings in Japan, we are unable to explain the direct impact of each treatment on clinical outcomes.

Obviously, this study has several limitations. First, the database lacks detailed information about patients' background, systemic disorders, and ocular diseases. As the health and socioeconomic status of older adults with diabetes is likely to be heterogenous from robust to frail, the treatment strategy for older patients with DME would be individualized. Accordingly, if detailed information had been recorded, some underlying problems specific for aged patients with DME could have been identified. Second, selection bias exists because the database contains data only from patients who completed a 2 year follow-up after initial treatment. Some might have returned to local physicians before 2 years with good response to treatment and no recurrence of macular edema, and others would have been lost to follow-up due to various reasons. Third, the database we utilized does not include detailed information on lens status which potentially affects the visual outcomes. We had noticed this problem and tried to minimize it by selecting the change in BCVA (not absolute BCVA value) for the primary outcome. Fourth, we were unable to analyze the relationship between glycemic control and treatment outcomes because of the lack of the detailed data on glycemic control during the 2 year period. Lastly, the availability of some anti-VEGF agents would affect the outcomes as discussed previously[16,19]. In Japan, approval of ranibizumab and aflibercept therapy for DME were granted in February 2014 and November 2014, respectively.

In conclusion, our secondary analysis of the STREAT-DME study conducted by the J-CREST group for the first time exhibited the effect of aging on treatment selection and outcomes in eyes with DME. Compared with younger patients with DME, patients with DME aged ≥75 years would be less frequently treated with anti-VEGF therapy, local corticosteroid injection, PPV, and outside PC and show insufficient improvement in BCVA. Some unanswered questions, including the impact of the heterogenous background status of aged patients with DME on visual outcomes, should be further examined in future studies.

ACKNOWLEDGMENTS

The authors would like to thank Katsunori Shimada, PhD, working in STATZ Institute Inc. for performing statistical analyses. This work was supported by Bayer, Japan (to S. Kusuhara), and clinical research grant-in-aid by Tokyo Medical University.

DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: Institutional review board approval was granted at each institution.
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

REFERENCES

1. https://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2019-Highlights.pdf. Accessed April 29, 2021.
2. Longo M, Bellastella G, Maiorino MI, *et al*. Diabetes and aging: from treatment goals to pharmacologic therapy. *Front Endocrinol (Lausanne)* 2019; 10: 45.
3. Aljied R, Aubin MJ, Buhrmann R, *et al*. Prevalence and determinants of visual impairment in Canada: Cross-sectional data from the Canadian longitudinal study on aging. *Can J Ophthalmol* 2018; 53: 291–297.
4. Huang ES, Laiteerapong N, Liu JY, *et al*. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. *JAMA Intern Med* 2014; 174: 251–258.
5. Nguyen QD, Brown DM, Marcus DM, *et al*. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012; 119: 789–801.
6. Schmidt-Erfurth U, Lang GE, Holz FG, *et al*. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. *Ophthalmology* 2014; 121: 1045–1053.
7. 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: 2044–2052.
8. 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: 1351–1359.
9. Stewart MW. Treatment of diabetic retinopathy: recent advances and unresolved challenges. *World J Diabetes* 2016; 7: 333–341.
10. Ogura Y, Shiraga F, Terasaki H, *et al*. Clinical practice pattern in management of diabetic macular edema in Japan: survey results of Japanese retinal specialists. *Jpn J Ophthalmol* 2017; 61: 43–50.
11. Holekamp NM, Campbell J, Almony A, *et al*. Vision outcomes following anti-vascular endothelial growth factor treatment of diabetic macular edema in clinical practice. *Am J Ophthalmol* 2018; 191: 83–91.
12. Stefanickova J, Cunha-Vaz J, Ulbig M, *et al*. A noninterventional study to monitor patients with diabetic macular oedema starting treatment with ranibizumab (POLARIS). *Acta Ophthalmol* 2018; 96: e942–e949.
13. Ziemssen F, Wachtlin J, Kuehlewein L, *et al*. Intravitreal Ranibizumab therapy for diabetic macular edema in routine practice: two-year real-life data from a non-interventional, Multicenter Study in Germany. *Diabetes Ther* 2018; 9: 2271–2289.

14. Massin P, Creuzot-Garcher C, Kodjikian L, *et al*. Real-world outcomes with Ranibizumab 0.5 mg in patients with visual impairment due to diabetic macular edema: 12-month results from the 36-month BOREAL-DME study. *Ophthalmic Res* 2019; 62: 101–110.
15. Mitchell P, Sheidow TG, Farah ME, *et al*. Effectiveness and safety of ranibizumab 0.5 mg in treatment-naive patients with diabetic macular edema: results from the real-world global LUMINOUS study. *PLoS One* 2020; 15: e0233595.
16. Shimura M, Kitano S, Muramatsu D, *et al*. Real-world management of treatment-naive diabetic macular oedema in Japan: two-year visual outcomes with and without anti-VEGF therapy in the STREAT-DME study. *Br J Ophthalmol* 2020; 104: 1209–1215.
17. Durso SC. Using clinical guidelines designed for older adults with diabetes mellitus and complex health status. *JAMA* 2006; 295: 1935–1940.
18. Mooradian AD. Evidence-based management of diabetes in older adults. *Drugs Aging* 2018; 35: 1065–1078.
19. Shimura M, Kitano S, Muramatsu D, *et al*. Real-world management of treatment-naive diabetic macular oedema: 2-year visual outcome focusing on the starting year of intervention from STREAT-DMO study. *Br J Ophthalmol* 2020; 104: 1755–1761.
20. Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. *Endocr Rev* 2016; 37: 278–316.
21. 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: 615–625.
22. Gokhale M, Sturmer T, Buse JB. Real-world evidence: The devil is in the detail. *Diabetologia* 2020; 63: 1694–1705.
23. 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: 209–222.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Change in proportions of categorical visual acuity from baseline to 2 years in each age category.

Figure S2 | Distribution of change in visual acuity from baseline to 2 years across age categories.