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CLINICAL INVESTIGATION

Vision-related quality of life in Japanese patients with wet age-related macular degeneration treated with intravitreal aflibercept in a real-world setting

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Abstract

Purpose To evaluate vision-related quality of life (QoL) in wet age-related macular degeneration (wAMD) patients receiving intravitreal aflibercept (IVT-AFL).

Study design Prospective, observational Japanese postmarketing surveillance study.

Methods All decisions were made by the treating physician. QoL was assessed using the 25-item National Eye Institute-Visual Functioning Questionnaire (NEI-VFQ-25) composite score administered at baseline, 6 months, and 12 months (primary assessment). Secondary assessments included NEI-VFQ-25 subscale scores, resource use, and best-corrected visual acuity (BCVA; logarithm of the minimum angle of resolution [logMAR]).

Results In total, 576 patients (baseline), 555 patients (6 months), and 446 patients (12 months) were included. The mean (SD) number of IVT-AFL injections was 3.5 (1.2) at 6 months and 4.6 (2.2) at 12 months. The mean (SD) improvement from baseline in the NEI-VFQ-25 composite score was 3.1 (11.1) at 6 months and 2.7 (12.3) at 12 months ($P < .0001$). For the NEI-VFQ-25 subscale scores, the mean change was ≥ 4 (minimally important difference) for general vision, near vision, and mental health at 6 months, and for general vision and mental health at 12 months (all $P < .0001$). A significant improvement from baseline was found in mean BCVA (logMAR) at 6 months (-0.1) and 12 months (-0.1) ($P < .0001$). The mean change from baseline in the NEI-VFQ-25 scores was greatest in patients with improved BCVA (gain of ≤ -0.3 logMAR units or ≥ 15 letters) after treatment.

Conclusion IVT-AFL was associated with significant improvements in QoL and visual acuity in Japanese patients with wAMD in a real-world setting.

Keywords Intravitreal aflibercept · NEI-VFQ-25 · Wet age-related macular degeneration · J-PMS

Introduction

Approximately 700,000 adults in Japan have age-related macular degeneration (AMD), a sight-threatening condition [1–5]. Most of the visual impairment is associated with the wet form of the disease (wAMD) [6], with the impact of wAMD on quality of life (QoL) being comparable to that observed for serious systemic diseases, such as cancer and ischemic heart disease [7]. Identifying ways to eliminate the burden associated with wAMD and to improve QoL through medical advances is a key issue in Japan because global estimates suggest that there will be more cases of AMD in Asia than in the rest of the world combined by 2050 [8, 9].

A growing awareness of the role that vascular endothelial growth factor (VEGF) plays in the development and

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progression of wAMD [10] has resulted in this protein becoming an important therapeutic target for blindness prevention. The development and widespread use of anti-VEGF agents has changed the paradigm of treatment for wAMD, and Japanese guidelines recommend these agents as a first choice in typical wAMD [11].

Anti-VEGF agents have been shown in international studies to improve both the vision-related outcomes and the QoL of wAMD patients [12–14]. In the VIEW 2 study, vision maintenance (ie, loss of < 15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) was also observed in Japanese patients with wAMD treated with intravitreal aflibercept (IVT-AFL) (100.0%; n = 70/70) or ranibizumab (95.8%; n = 23/24) at 12 months [15].

The impact of anti-VEGF agents on QoL has been specifically examined using validated instruments, such as the 25-item National Eye Institute-Visual Functioning Questionnaire (NEI-VFQ-25). The NEI-VFQ-25 is a vision-targeted QoL measure that was developed in the mid-1990s and has been widely translated and used. The NEI-VFQ-25 was administered at baseline and after 12 months of IVT-AFL or ranibizumab treatment in patients with wAMD randomized in the pivotal VIEW studies [12]. Outcomes were comparable across all NEI-VFQ-25 subscales for IVT-AFL 2 mg bimonthly (2q8) and ranibizumab 0.5 mg monthly. However, to our knowledge, no multicenter studies have assessed IVT-AFL treatment using the NEI-VFQ-25 in Japanese patients with wAMD in a real-world setting. To address this, an observational QoL survey was conducted as part of the Japan postmarketing surveillance of IVT-AFL (J-PMS). Herein, we report the outcomes from this 12-month study.

Patients and methods

Study design

This was a multicenter, prospective, cross-sectional, observational J-PMS study (NCT01756261) to evaluate the effectiveness of IVT-AFL in Japanese patients with wAMD on the basis of QoL assessments. Patients were enrolled from 61 sites in Japan from 26 December 2012 (first patient, first visit) to 20 July 2016 (last patient, last visit). The study was conducted in accordance with Good Post-marketing Study Practice [16] and in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation. No institutional review board (IRB) approval was formally required for this type of study (J-PMS), but IRB approval was obtained in accordance with the institutional requirements. All the patients provided written informed consent before participation.

Participants

Adults with a diagnosis of subfoveal choroidal neovascularization (CNV) secondary to wAMD who had not been treated with IVT-AFL or another anti-VEGF agent were eligible. The treated eye was defined as the study eye; if both eyes had wAMD, then the first treated eye or the worse-seeing eye (WSE) (if both were treated at the same time) was included. Patients were also required to be registered with the J-PMS for IVT-AFL in the wAMD registry and to be able to comply with all the investigations.

Treatment

To represent a real-world setting, all treatment decisions were made by the physician on the basis of his or her usual routine clinical practice and the patient's condition. IVT-AFL was administered in accordance with the prescribing information in Japan [17].

Assessments

QoL was assessed by the investigator by means of the Japanese version of the NEI-VFQ-25 questionnaire (v.1.4, interviewer-administered format) [18] at baseline (before treatment) and at 6 and 12 months after IVT-AFL treatment. The Japanese version was validated by patients with cataracts (before and after surgery), glaucoma, or AMD and by a representative sample from the general population (reference group); only minor modifications were required to provide reliable and valid data in Japan [18]. The NEI-VFQ-25 consists of 25 vision-targeted questions generating 12 subscales (summarized in Online Resource 1). Each subscale score was converted to a score between 0 and 100, with higher scores indicating better QoL. The composite score was the mean of all the item scores except that of general health. Resource use (IVT-AFL injections) and best-corrected visual acuity (BCVA) were documented at baseline and at 6 and 12 months. Visual acuity data were collected in decimal format and converted to logarithm of the minimum angle of resolution (logMAR) units by use of a published conversion chart [19].

The primary assessment was the mean change from baseline in the NEI-VFQ-25 composite score at 6 and 12 months after IVT-AFL treatment. Secondary assessments included the mean change from baseline to 6 and 12 months in the NEI-VFQ-25 subscale scores, resource use, and BCVA (logMAR) assessments. Outcomes were also assessed in the predefined subgroups. Safety outcomes were monitored and recorded in the registry but were not examined in this study.

Statistical analyses

A sample size of 705 patients, with the assumption that 600 patients would complete 12 months of treatment, was considered sufficient for the comparison of the NEI-VFQ-25 scores before and after IVT-AFL using a standard deviation of 25, with a power of 95%, and a 2-sided significance level of 5% ($P < .05$). Patients were eligible for QoL analysis if they completed NEI-VFQ-25 assessments at baseline and at 6 months or 12 months. This was defined as the full analysis set. Resource use and visual assessments were analyzed in all the populations.

A change from baseline of ≥ 4 for the NEI-VFQ-25 composite and subscale scores was regarded as clinically significant in this study. This threshold was based on a published study that found that a change in BCVA of 15 letters corresponded to an NEI-VFQ-25 composite score of 4 in patients with wAMD [20]. This score was regarded as the minimally important difference (MID) for the NEI-VFQ-25 score in wAMD [7].

The analyses were performed using summary statistics for continuous data (mean, standard deviation [SD]), and categorical data (frequency tables). The outcomes were reported with no adjustment for missing values (observed data). The primary assessment was analyzed using paired *t* tests, and secondary assessments were analyzed using paired *t* tests or 1-way analysis of variance for comparisons of ≥ 2 means.

Outcomes were also assessed in the subgroups. Baseline visual acuity was defined as good (> 70 letters or decimal visual acuity > 0.5) or poor (≤ 70 letters or decimal visual acuity ≤ 0.5) on the basis of the following formula: ETDRS letters = $85 + 50 \times \log_{10}$ (decimal visual acuity) = 69.9. The impact of the following factors on the NEI-VFQ-25 assessments at 6 and 12 months was determined: baseline visual acuity (> 70 or ≤ 70 letters); clinical characteristics and patient demographics (including sex, lesion type, laterality, duration of disease, treatment history, and age [defined as < 60, 60–< 70, 70–< 80, and ≥ 80 years]); BCVA categories (defined as improved [gain of ≤ -0.3 logMAR units or ≥ 15 letters], maintained [loss of < 0.3 logMAR units or < 15 letters], and deteriorated [loss of ≥ 0.3 logMAR units or ≥ 15 letters]); and injections (based on the number of injections at 12 months [1–3, 4–5, 6–8, ≥ 9 injections]).

All statistical analyses were performed using the software package SAS release 9.1 or higher (SAS Institute, Cary, NC, USA).

Results

Patients

The patients' characteristics are shown in Figure 1. Overall, 754 patients were screened and 685 patients were treated with IVT-AFL. NEI-VFQ-25 questionnaires were not initiated in 47 patients, and incomplete responses were reported in 62 patients. Valid questionnaires were analyzed from 576 patients at baseline, from 555 patients at 6 months, and from 446 patients at 12 months. The baseline characteristics (n = 576) are shown in Table 1. The mean age was 73.4 years (range 46–95 years), and most patients were male (69.6%) with unilateral wAMD (92.2%). The BCVA (logMAR) was 0.4 and the NEI-VFQ-25 composite score was 76.9 at baseline.

Resource use

The mean (SD) number of IVT-AFL injections at 6 months was 3.5 (1.2) (n = 555), and the mean (SD) number of injections at 12 months was 4.6 (2.2) (n = 446). A breakdown of the mean number of injections received at 12 months is shown in Table 2a. The proportion of patients (n = 446) in

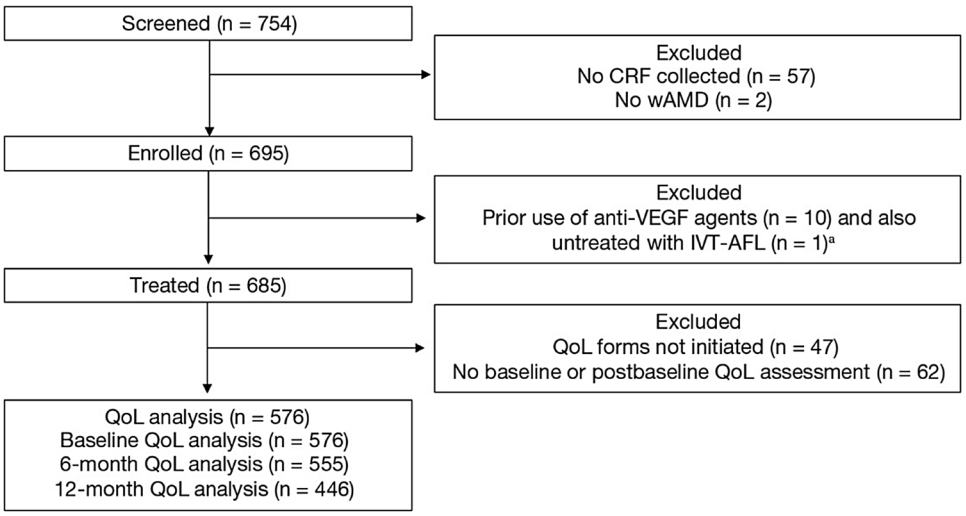

Fig. 1 Patient disposition during the study. *CRF* case report form, *IVT-AFL* intravitreal aflibercept, *QoL* quality of life, *VEGF* vascular endothelial growth factor, *wAMD* wet age-related macular degeneration. [a]One patient had previous treatment with anti-VEGF agents and no IVT-AFL treatment

Table 1 Baseline and clinical characteristics

Mean (SD), unless stated	Patients (N = 576)
Age, y[a]	73.4 (8.7)
< 60, n (%)	33 (5.7)
60–< 70, n (%)	153 (26.6)
70–< 80, n (%)	240 (41.7)
≥ 80, n (%)	150 (26.0)
Male, n (%)	401 (69.6)
Eye(s) with wAMD, n (%)	
Unilateral	531 (92.2)
Bilateral	45 (7.8)
wAMD duration, mo (n = 224)	13.6 (28.8)
wAMD duration categories, mo, n (%)	
< 2	78 (13.5)
2–< 6	65 (11.3)
6–< 12	24 (4.2)
≥ 12	57 (9.9)
Unknown	352 (61.1)
wAMD subtype, n (%) (study eyes)	
Typical AMD[b]	316 (54.9)
Polypoidal choroidal vasculopathy	245 (42.5)
Retinal angiomatous proliferation	15 (2.6)
Pretreatment, n (%) (n = 27)	
Photodynamic therapy	14 (51.9)
Surgery	6 (22.2)
Photocoagulation	5 (18.5)
Photodynamic therapy and photocoagulation	1 (3.7)
Photodynamic therapy and surgery	1 (3.7)
BCVA (logMAR) (n = 574)	0.4 (0.4)
NEI-VFQ-25 composite score	76.9 (14.2)

BCVA best-corrected visual acuity, *CNV* choroidal neovascularization, *logMAR* logarithm of the minimum angle of resolution, *NEI-VFQ-25* 25-item National Eye Institute-Visual Functioning Questionnaire, *SD* standard deviation, *(w)AMD* (wet) age-related macular degeneration

[a]Age subgroups were selected on the basis of age distribution (mean [SD]: 73.5 [8.8] years, range: 49–95 years)

[b]Typical AMD was defined as the total of occult CNV and minimally classic CNV

each injection group was 40.4% (1–3 injections), 28.0% (4–5 injections), 26.7% (6–8 injections), and 4.9% (≥ 9 injections) at 12 months.

Functional (QoL) assessments

NEI-VFQ-25 composite score (primary outcome)

The mean (SD) improvement from baseline in the NEI-VFQ-25 composite score was 3.1 (11.1) at 6 months (n = 555) and 2.7 (12.3) at 12 months (n = 446) ($P < .0001$ at both time points) during IVT-AFL treatment.

NEI-VFQ-25 subscale scores

For the NEI-VFQ-25 subscale scores, the mean change from baseline was ≥ 4 (MID) for general vision, near vision, and mental health at 6 months (all $P < .0001$) and for general vision and mental health at 12 months (both $P < .0001$; Table 3). Significant improvements ($P < .05$) were also found for general health, distant vision, social functioning, role limitations, dependency on others, and peripheral vision at 6 months and for general health, near vision, distant vision, social functioning, role limitations, and dependency on others at 12 months. Negative changes were found for ocular pain, driving, and color vision at 12 months, but no significant differences were observed from baseline.

Demographic subgroups

The NEI-VFQ-25 composite scores by demographic subgroups are shown in Table 4a. No significant differences between subgroups were found in terms of sex, lesion subtype, unilateral/bilateral disease, disease duration, or treatment history. The mean change was ≥ 4 (MID) for disease duration (< 2 months, 2–< 6 months, and ≥ 12 months duration) and for patients with previous wAMD treatment at 6 months, and for disease duration (< 2 months' and ≥ 12 months' duration) and bilateral disease but not unilateral disease at 12 months. The age group subanalysis showed that overall, patients aged 80 years or older had the lowest NEI-VFQ-25 composite score at baseline and the changes in the NEI-VFQ-25 composite score at 6 months and 12 months were also marginal when compared with those of the other age groups, which resulted in a decrease in the overall NEI-VFQ-25 composite score at 6 months and 12 months.

Number of injections

A significant improvement in the NEI-VFQ-25 composite score from baseline to 6 and 12 months was found across all the injection groups except the group receiving ≥ 9 injections at 12 months; this mean (SD) improvement was greatest in patients receiving 6 to 8 injections at 6 months: 4.7 ([11.3]; $P < .0001$) and 12 months: 3.6 ([12.9]; $P < .01$; Fig. 2).

Visual assessments

The mean BCVA (logMAR) was significantly improved at 6 months (-0.1) and 12 months (-0.1) ($P < .0001$ at both time points) during IVT-AFL treatment (Table 4b). Similar improvements were observed in patients with typical AMD (occult and minimally classic CNV) and polypoidal

Table 2 Distribution of (a) injections and (b) BCVA categories over 12 months

(a)	6 months	12 months
Number of IVT-AFL injections at 12 months, mean (SD)		
	n = 555	n = 446
1–3 injections	2.5 (0.7) (n = 250)	2.6 (0.7) (n = 180)
4–5 injections	3.9 (0.7) (n = 140)	4.5 (0.5) (n = 125)
6–8 injections	4.6 (0.7) (n = 141)	6.8 (0.7) (n = 119)
≥ 9 injections	5.4 (0.9) (n = 24)	9.9 (1.4) (n = 22)
(b)	6 months	12 months
BCVA categories at each time point, n (%)[a]		
	n = 280	n = 209
Improved	61 (21.8)	49 (23.4)
Maintained	206 (73.6)	147 (70.3)
Deteriorated	13 (4.6)	13 (6.2)
BCVA categories in patients with good baseline visual acuity (> 70 letters), n (%)[a]		
	n = 130	n = 88
Improved	2 (1.5)	3 (3.4)
Maintained	126 (96.9)	80 (90.9)
Deteriorated	2 (1.5)	5 (5.7)
BCVA categories in patients with poor baseline visual acuity (≤ 70 letters), n (%)[a]		
	n = 150	n = 121
Improved	59 (39.3)	46 (38.0)
Maintained	80 (53.3)	67 (55.4)
Deteriorated	11 (7.3)	8 (6.6)

BCVA best-corrected visual acuity, *IVT-AFL* intravitreal aflibercept, *logMAR* logarithm of the minimum angle of resolution, *SD* standard deviation

[a]Data not available for all the patients. Improved, gain of ≤ -0.3 logMAR units or ≥ 15 letters; Maintained, loss of < 0.3 logMAR units or < 15 letters; Deteriorated, loss of ≥ 0.3 logMAR units or ≥ 15 letters

Table 3 Mean change in NEI-VFQ-25 subscale scores from baseline to 6 and 12 months after IVT-AFL treatment (observed data set)[a]

Subscale score	Baseline			Change from baseline at 6 months				Change from baseline at 12 months			
	n	Mean	SD	n	Mean	SD	*P* value[b]	n	Mean	SD	*P* value[b]
General health	575	48.7	19.4	552	2.2	20.5	.0132	443	2.5	20.9	.0129
General vision	575	62.8	17.1	553	6.7	18.6	< .0001	445	6.7	19.0	< .0001
Ocular pain	576	86.9	16.4	555	0.7	16.1	.3085	446	-0.2	17.9	.8173
Difficulty with near-vision activities	576	66.0	23.7	553	4.2	22.5	< .0001	445	3.6	23.4	.0011
Difficulty with distance-vision activities	576	76.7	18.8	555	2.9	17.1	< .0001	446	3.5	18.6	< .0001
Limitation of social functioning due to vision	553	84.3	18.9	519	1.6	18.2	.0475	413	2.1	17.9	.0196
Mental health problems due to vision	576	71.1	23.2	555	6.9	19.3	< .0001	446	6.4	20.7	< .0001
Role limitations due to vision	575	76.0	24.0	554	3.3	23.5	.0009	446	3.3	22.8	.0024
Dependency on others due to vision	576	84.0	21.2	555	2.9	18.2	.0002	446	3.0	18.5	.0008
Driving difficulties	357	74.7	25.0	344	1.2	19.9	.2780	270	-1.3	23.5	.3838
Difficulty with color vision	515	91.6	14.0	490	0.5	15.3	.5064	393	-1.1	16.8	.2017
Difficulty with peripheral vision	567	76.1	21.3	543	2.0	22.6	.0419	433	1.6	23.7	.1724

IVT-AFL intravitreal aflibercept, *NEI-VFQ-25* 25-item National Eye Institute-Visual Functioning Questionnaire, *SD* standard deviation

[a]Data not available for all the patients

[b]Paired *t* test (vs baseline)

Table 4 Changes in (a) NEI-VFQ-25 composite score and (b) BCVA after IVT-AFL treatment in subgroups (observed data set)[a]

(a)		Baseline			Change from baseline at 6 months				Change from baseline at 12 months			
		n	Mean	SD	n	Mean	SD	*P* value[b]	n	Mean	SD	*P* value[b]
Sex	Male	401	76.8	14.4	388	3.1	11.1	.9068	309	2.3	12.2	.2570
	Female	175	77.2	13.8	167	3.0	11.2		137	3.7	12.6	
Age[c]	< 60, n (%)	33	80.4	12.5	31	3.7	12.5	.1624	26	3.6	13.7	.3106
	60–< 70, n (%)	153	80.4	11.7	147	3.5	8.4		116	3.6	10.1	
	70–< 80, n (%)	240	75.9	14.5	231	3.9	12.2		192	3.1	12.3	
	≥ 80, n (%)	150	74.3	15.8	146	1.3	11.3		112	0.8	14.1	
Lesion subtype	Typical AMD	316	76.2	14.0	304	3.2	11.5	.1432	239	2.8	12.4	.8715
	Polypoidal choroidal vasculopathy	245	77.8	14.3	236	3.4	10.5		194	2.7	12.3	
	Retinal angiomatous proliferation	15	77.8	17.0	15	-2.4	12.9		13	1.0	12.5	
Eye(s) with wAMD	Unilateral	531	77.9	13.6	510	3.0	10.6	.6418	408	2.5	11.9	.1976
	Bilateral	45	66.2	17.1	45	3.8	16.5		38	5.2	16.3	
Disease duration	< 2 months	78	76.4	16.5	76	4.8	12.4	.4214	60	5.0	12.5	.8389
	2–< 6 months	65	77.2	13.1	62	4.5	11.4		53	3.1	13.1	
	6–< 12 months	24	75.4	14.7	24	1.2	10.1		20	3.6	8.0	
	≥ 12 months	57	77.3	13.7	55	5.6	8.1		48	4.4	9.9	
	Unknown	352	77.1	14.0	338	2.2	11.2		265	1.7	12.8	
Treatment history of wAMD	No	534	77.0	14.1	514	2.9	11.1	.2169	415	2.7	12.3	.6370
	Yes	27	77.6	14.9	26	5.7	10.2		22	3.9	11.2	

(b)		Time point	BCVA, logMAR			Change from baseline, logMAR		
			Eyes	Mean	SD	Mean	SD	*P* value[b]
	Total	Baseline	574	0.4	0.4	–	–	
		6 months	284	0.3	0.4	-0.1	0.2	< .0001
		12 months	235	0.3	0.4	-0.1	0.3	< .0001
Lesion subtype	Typical AMD	Baseline	315	0.5	0.4	–	–	
		6 months	139	0.3	0.4	-0.1	0.3	< .0001
		12 months	122	0.3	0.4	-0.1	0.3	.0001
	Polypoidal choroidal vasculopathy	Baseline	244	0.4	0.4	–	–	
		6 months	140	0.2	0.3	-0.1	0.2	< .0001
		12 months	109	0.2	0.4	-0.1	0.2	< .0001
	Retinal angiomatous proliferation	Baseline	15	0.5	0.4	–	–	
		6 months	5	0.3	0.1	-0.4	0.3	.0648
		12 months	4	0.7	0.5	0.1	0.5	.7159
No. of injections at 12 months	1–3 injections	Baseline	260	0.4	0.4	–	–	
		6 months	86	0.3	0.4	-0.1	0.3	< .0001
		12 months	58	0.3	0.4	-0.1	0.2	.0003
	4–5 injections	Baseline	148	0.4	0.4	–	–	
		6 months	80	0.3	0.4	-0.1	0.2	< .0001
		12 months	58	0.3	0.4	-0.2	0.3	.0001
	6–8 injections	Baseline	142	0.4	0.4	–	–	
		6 months	102	0.2	0.3	-0.1	0.2	< .0001
		12 months	99	0.3	0.4	-0.1	0.3	.0004
	≥ 9 injections	Baseline	24	0.3	0.3	–	–	
		6 months	16	0.2	0.3	-0.1	0.2	.0884
		12 months	20	0.2	0.3	-0.1	0.3	.0657

BCVA best-corrected visual acuity, *IVT-AFL* intravitreal aflibercept, *logMAR* logarithm of the minimum angle of resolution, *NEI-VFQ-25* 25-item National Eye Institute-Visual Functioning Questionnaire, *SD* standard deviation, *(w)AMD* (wet) age-related macular degeneration

[a]Data not available for all the patients

[b]*t* test (vs baseline) for NEI-VFQ-25 and 1-way analysis of variance (vs baseline) (does not include unknown values) for BCVA

[c]Age subgroups were selected on the basis of age distribution (mean [SD]: 73.5 [8.8] years, range: 49–95 years)

Decrease = improvement on logMAR scale

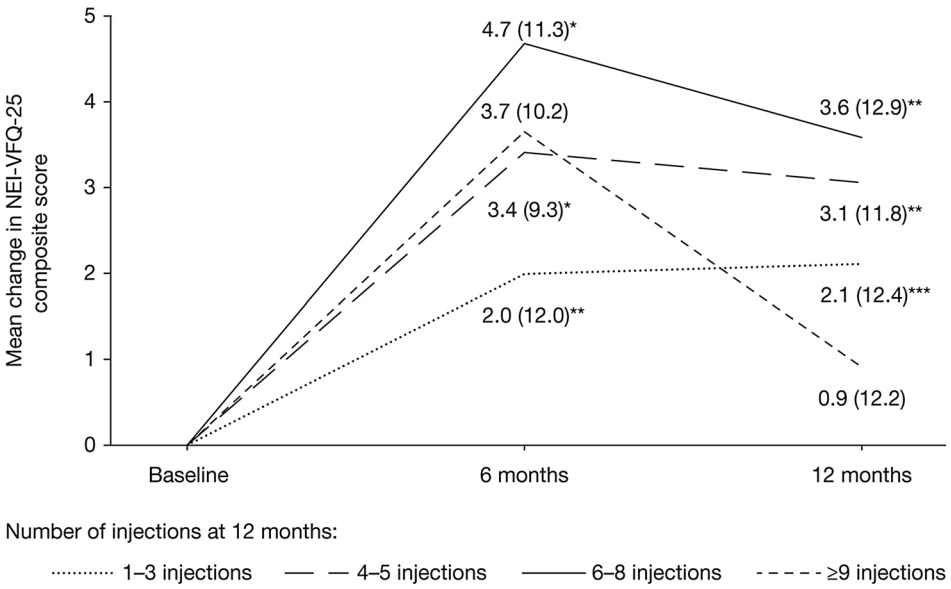

Fig. 2 Mean (SD) change in the NEI-VFQ-25 composite score from baseline to 12 months after IVT-AFL treatment based on the number of injections (observed data set). *IVT-AFL* intravitreal aflibercept, *NEI-VFQ-25* 25-item National Eye Institute-Visual Functioning Questionnaire, *SD* standard deviation. *$P < .0001$; **$P < .01$; ***$P < .05$ versus baseline (paired *t* test). Number of injections at 12 months: 1–3 (n = 250 [6 months], n = 180 [12 months]), 4–5 (n = 140, n = 125), 6–8 (n = 141, n = 119), ≥ 9 (n = 24, n = 22)

choroidal vasculopathy. The BCVA improvements were also significant and consistent across most of the injection groups, with no obvious trends (Table 4b).

The BCVA categories were also improved or maintained in the majority of patients at 6 months (95.4%) and at 12 months (93.8%; Table 2b). Most patients with good visual acuity at baseline (> 70 letters) maintained their BCVA at 12 months (90.9%) with treatment. The BCVA was improved (38.0%) or maintained (55.4%) at 12 months in patients who had poor visual acuity at baseline (≤ 70 letters; Table 2b).

Patients with improved/maintained BCVA experienced significantly greater mean (SD) improvements (5.7 [9.7]/3.9 [10.7]; both $P < .0001$) in the NEI-VFQ-25 composite score at 6 months than did patients whose BCVA deteriorated (-0.2 [9.7]); these improvements were generally maintained at 12 months (Fig. 3). Similarly, the mean (SD) change in the NEI-VFQ-25 composite score was greatest in patients with good baseline visual acuity (> 70 letters) who experienced improved BCVA at 6 months (18.5 [25.1]) and 12 months (8.4 [26.8]) when compared with the other groups (Fig. 4). When the NEI-VFQ-25 subscale scores were stratified by baseline visual acuity, the evidence indicated that poor baseline visual acuity was associated with negative NEI-VFQ-25 scores

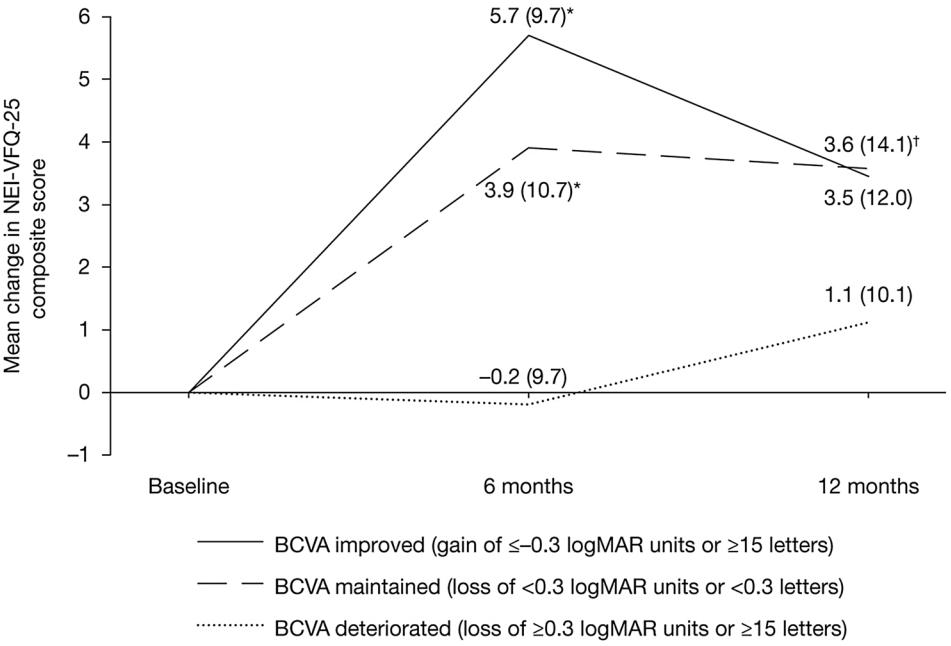

Fig. 3 Mean (SD) change in the NEI-VFQ-25 composite score from baseline to 12 months after IVT-AFL treatment based on BCVA categories at each time point (observed data set). *BCVA* best-corrected visual acuity, *IVT-AFL* intravitreal aflibercept; *logMAR* logarithm of the minimum angle of resolution, *NEI-VFQ-25* 25-item National Eye Institute-Visual Functioning Questionnaire, *SD* standard deviation. *$P < .0001$; †$P < .001$ versus baseline (paired *t* test). BCVA categories: improved (n = 61 [6 months], n = 49 [12 months]), maintained (n = 206, n = 147), deteriorated (n = 13, n = 13)

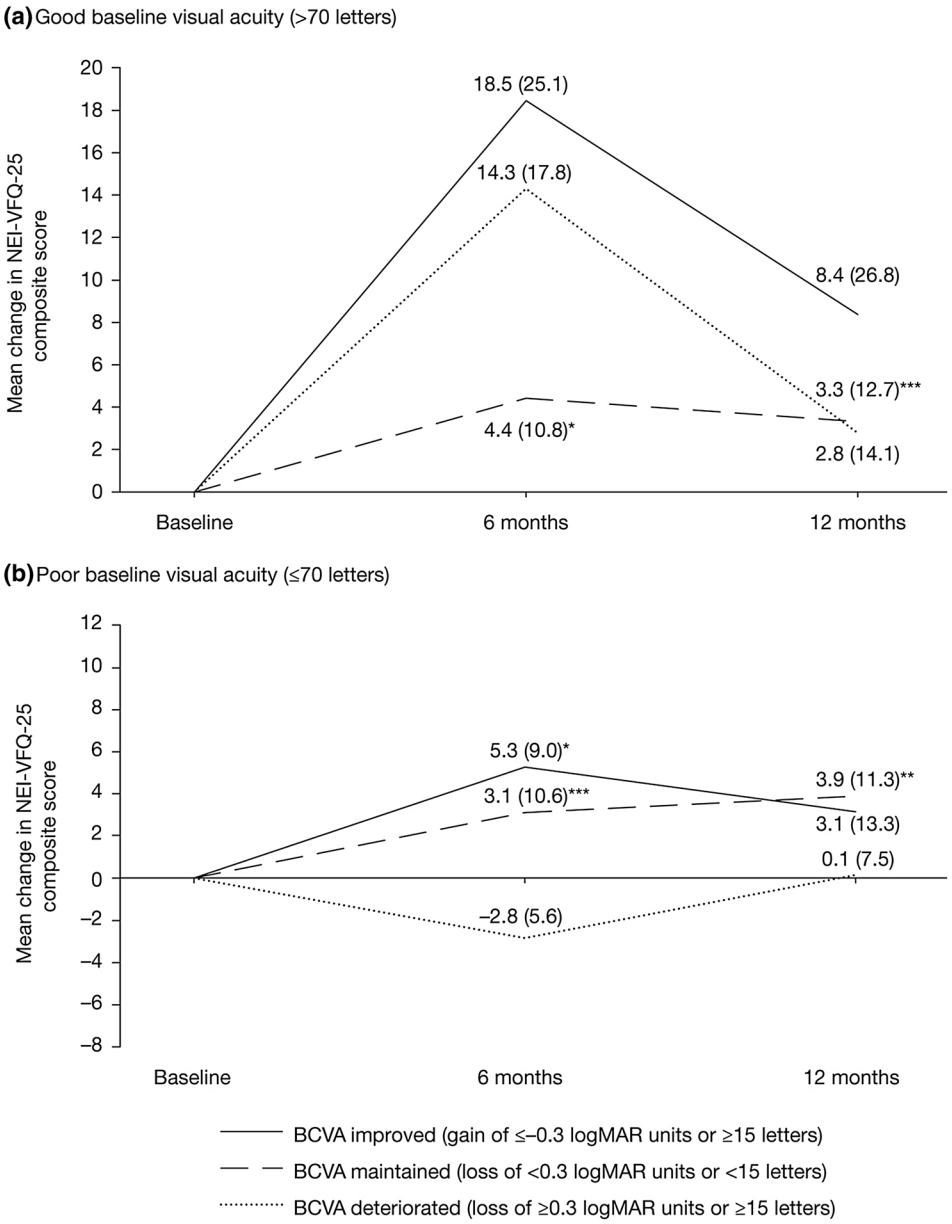

Fig. 4 Mean (SD) change in the NEI-VFQ-25 composite score from baseline to 12 months after IVT-AFL treatment based on BCVA categories at each time point in patients with (**a**) good (> 70 letters) or (**b**) poor (≤ 70 letters) baseline visual acuity (observed data set). *BCVA* best-corrected visual acuity, *IVT-AFL* intravitreal aflibercept, *logMAR* logarithm of the minimum angle of resolution, *NEI-VFQ-25* 25-item National Eye Institute-Visual Functioning Questionnaire, *SD* standard deviation. *$P < .0001$; **$P < .01$; ***$P < .05$ versus baseline (paired *t* test). BCVA categories (a) improved (n = 2 [6 months], n = 3 [12 months]), maintained (n = 126, n = 80), deteriorated (n = 2, n = 5), and (b) improved (n = 59, n = 46), maintained (n = 80, n = 67), deteriorated (n = 11, n = 8). Note: the sample size in the BCVA deterioration category is small and these results should be interpreted with caution

for ocular pain (-1.1), driving difficulties (-2.2), and color vision (-1.1) at 12 months (Fig. 5).

Discussion

This observational J-PMS study showed that IVT-AFL was associated with significant improvements in QoL (composite NEI-VFQ-25 score: 2.7) and visual acuity (~ 6.5 letters) at 12 months in patients with wAMD in a real-world setting. The mean changes in most of the NEI-VFQ-25 subscale scores (9 of 12 [6 months] and 8 of 12 [12 months]) were also significant ($P < .05$), but some were lower than the MID score (≥ 4) defined previously [7, 20]. Importantly, however, the MID score corresponded to a 15-letter change in BCVA [7, 20]. When the NEI-VFQ-25 composite score was stratified according to BCVA categories, the mean change in the NEI-VFQ-25 composite score was 5.7 at 6 months and 3.5 at 12 months for patients who experienced an improvement in BCVA (gain of ≤ -0.3 logMAR units or ≥ 15 letters). The greatest improvement was observed in patients with good baseline visual acuity (> 70 letters) and an improvement in BCVA with treatment; in this category, the mean change in the NEI-VFQ-25 composite score was 18.5 (6 months) and 8.4 (12 months). It is also important to note that the baseline NEI-VFQ-25 composite score in our study (76.9) was higher than in the randomized studies described below, and this may have resulted in smaller gains for the composite score.

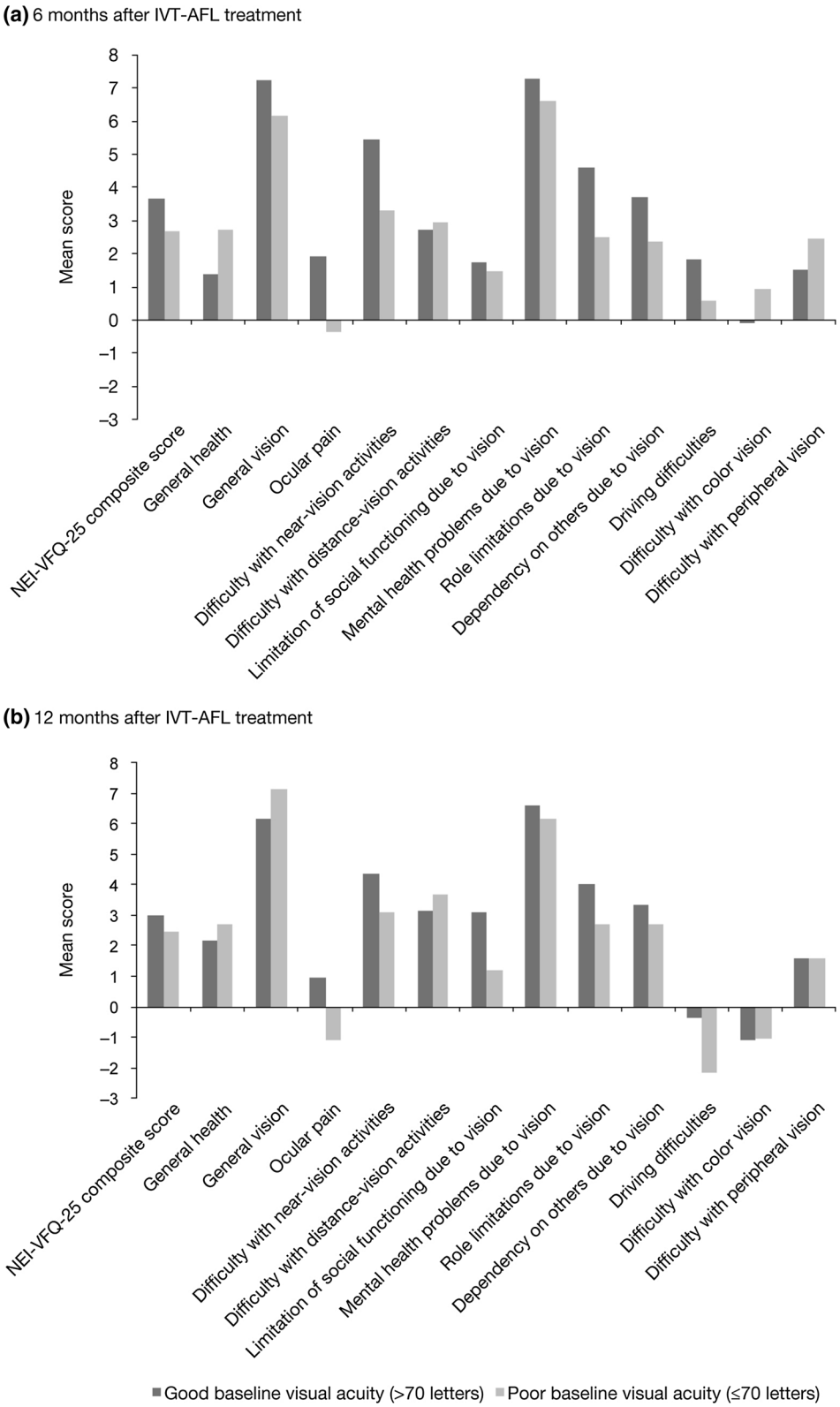

Fig. 5 Mean change in NEI-VFQ-25 composite and subscale scores from baseline to (**a**) 6 months and (**b**) 12 months after IVT-AFL treatment in patients with good (> 70 letters) or poor (≤ 70 letters) baseline visual acuity (observed data set). *IVT-AFL* intravitreal aflibercept, *NEI-VFQ-25* 25-item National Eye Institute-Visual Functioning Questionnaire. (a) Patient numbers by subscale for good (n = 240, n = 239, n = 240, n = 240, n = 239, n = 240, n = 232, n = 240, n = 239, n = 240, n = 165, n = 219, n = 234) and poor baseline visual acuity (n = 313, n = 311, n = 311, n = 313, n = 312, n = 313, n = 285, n = 313, n = 313, n = 313, n = 178, n = 270, n = 307). (b) Patient numbers by subscale for good (n = 198, n = 195, n = 198, n = 198, n = 197, n = 198, n = 191, n = 198, n = 198, n = 198, n = 139, n = 179, n = 192) and poor baseline visual acuity (n = 248, n = 248, n = 247, n = 248, n = 248, n = 248, n = 222, n = 248, n = 248, n = 248, n = 131, n = 214, n = 241)

In the IVT-AFL 2q8 group of the VIEW studies, the mean baseline NEI-VFQ-25 composite score was 70.4, and the mean change was 5.0 at 12 months, which exceeded the MID score (≥ 4); the improvement in BCVA was 8.4 ETDRS letters [13, 14]. These outcomes were higher than those observed in the current study and may reflect stricter

adherence to the 2q8 IVT-AFL regimen in a randomized setting. A pooled analysis of the MARINA and ANCHOR studies (ranibizumab 0.3 mg and 0.5 mg, respectively) showed that a 15-letter change in BCVA over 12 months corresponded to a 4- to 6-point increase in the NEI-VFQ-25 composite score from a mean baseline score of 69.3 (MARINA; n = 716) and 69.9 (ANCHOR; n = 418) [20]. Similar outcomes were observed in 3 prespecified subscale scores (near activities, distant activities, and vision-specific dependency). We also analyzed these 3 subscales according to BCVA categories and found that an improvement in BCVA (gain of ≤ -0.3 logMAR units or ≥15 letters) at 12 months corresponded to a ~ 5- to 10-point increase in these subscale scores (Online Resource 2). Of additional interest in our study was the possible association between poor baseline visual acuity (≤ 70 letters) and decreases in some subscale scores (ocular pain, driving difficulties, and color vision).

In another observational study of 267 patients with wAMD treated with ranibizumab 0.5 mg (HELIOS), the mean change in visual acuity was 1.6 ETDRS letters (baseline: 56.3 letters); the NEI-VFQ-25 composite score was 1.9 (baseline: 67.0), and only 43.8% of patients achieved an MID score greater than 4.3 at 12 months [21]. These findings are lower than those observed in the MARINA and ANCHOR studies and indicate the difficulties of repeating visual acuity and QoL outcomes achieved with strict protocols in randomized studies in real-world settings. This may be partly explained by the injection frequency: in the HELIOS study, the mean number of ranibizumab injections was 5.0 over 12 months, which was lower than the monthly injections in the MARINA and ANCHOR studies.

The mean number of IVT-AFL injections used in our study was also low, and the use of a loading dose (3 initial monthly injections) plus a bimonthly (2q8) regimen may have improved the outcomes as indicated by the outcomes in the VIEW studies [13]. There was a trend toward increased NEI-VFQ-25 composite scores with more injections, but patients receiving ≥ 9 injections at 12 months showed a decline. This may have been affected by the small patient number (n = 22) and was possibly due to the severity of the patients' conditions.

Some findings should be interpreted with caution owing to the small patient numbers in the subgroups. It is also important to note that the analyses were not based on the best-seeing eye (BSE) or WSE. Previous studies suggested that the BSE is the most important contributor to monitoring the treatment effect on visual functioning and QoL, but the WSE also contributes. The mean change in the NEI-VFQ-25 composite score following 24 months of ranibizumab 0.5 mg treatment was 7.5 (BSE) and 1.7 (WSE) in the 646 patients with wAMD enrolled in the MARINA study and 13.3 (BSE) and 2.6 (WSE) in the 379 patients with wAMD enrolled in the ANCHOR study [22]. Overall, our study design was meant to assess the treated eye, and therefore, the visual acuity data of the fellow eyes were not always collected, and some centers also had missing data. Therefore, we could not perform analysis according to the BSE or WSE. The fact that we included the treated eye or the WSE rather than the BSE (if both were treated) may explain why some scores were lower than the MID score of ≥ 4. Finally, it should be noted that the dosing regimen (PRN, fixed dosing, or treat and extend) may have an impact on the QoL outcomes. However, this information was not included in the questionnaire used to collect the data for this study, so we were unable to analyze the results on the basis of the dosing regimen.

In conclusion, this is the first large-scale study to examine QoL outcomes in patients with wAMD treated with IVT-AFL under real-world conditions in Japan. It also considered the impact of different baseline characteristics and clinical factors, including visual acuity categories and injection groups. We showed that IVT-AFL was associated with significant improvements in QoL and visual acuity in patients with wAMD in this setting. We also identified an association between NEI-VFQ-25 score, baseline visual acuity, and improvements in BCVA over time. Several key NEI-VFQ-25 subscale scores also exceeded the MID threshold. Although the use of an IVT-AFL loading dose (3 initial monthly injections) and a bimonthly regimen may have resulted in greater QoL gains over 12 months, the findings were positive and consistent with those observed in randomized studies such as the VIEW studies.

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Conflicts of interest F. Gomi, Honorarium (Bayer, Alcon, Novartis, Santen, Senju), Speaker fee (Alcon, Bayer, Santen, Senju), Advisory board fee (Alcon, Bayer, Senju), Grant (Alcon, Bayer, Johnson and

Johnson, Nidek, Novartis, Pfizer, Santen, Senju), H. Migita, Employee (Bayer); T. Sakaguchi, Employee (Bayer); H. Okada, Consultant fee (Bayer); T. Sugawara, Consultant fee (Bayer); Y. Hikichi, Employee (Bayer).

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