Annals of Clinical Epidemiology

ORIGINAL ARTICLE

Patterns of anti-vascular endothelial growth factor treatment for chorioretinal vascular diseases: Analysis of a nationwide claims database in Japan

Fumi Gomi[1,*], Ryo Kawasaki[2,*], Yuichiro Ogura[3], Kosuke Iwasaki[4], Tomomi Takeshima[4], Masafumi Yamabe[5], Kota Imai[5]

ABSTRACT

BACKGROUND

Although intravitreal anti-vascular endothelial growth factor therapy is currently considered the first-line treatment for chorioretinal vascular diseases in Japan, information regarding its treatment pattern is scarce. This study investigated the patterns of anti-vascular endothelial growth factor treatment for chorioretinal vascular diseases.

METHODS

A health insurance claims database from acute care hospitals was used to estimate treatment intervals and continuation and drop-out rates regarding the anti-vascular endothelial growth factor. Patients aged ≥50 years diagnosed with neovascular age-related macular degeneration or aged ≥18 years diagnosed with diabetic macular edema or retinal vein occlusion were analyzed.

RESULTS

Data were included for 76,535, 49,704, and 37,681 patients with neovascular age-related macular degeneration, diabetic macular edema, and retinal vein occlusion, respectively; exactly 8,111, 2,283, and 6,896 received the treatment, respectively. The mean and median interval ranges during the maintenance phase by treatment initiation year were 94–100 and 73–80, 111–120 and 98–102, and 97–103 and 87–93 days for neovascular age-related macular degeneration, diabetic macular edema, and retinal vein occlusion, respectively, without any trend over time. A tendency to increase the treatment continuation rate was indicated in later years by Kaplan–Meier curves. The drop-out rate in the treatment initiation year (2016) was 32% from 63% (2009), 53% from 69% (2014), and 36% from 47% (2013) for neovascular age-related macular degeneration, diabetic macular edema, and retinal vein occlusion, respectively.

CONCLUSIONS

For all these diseases, the treatment intervals did not change remarkably, and a tendency toward improved treatment continuation was suggested.

KEY WORDS

anti-vascular endothelial growth factor, diabetic macular edema, intravitreal injections, neovascular age-related macular degeneration, retinal vein occlusion

[1] Department of Ophthalmology, Hyogo Medical University
[2] Department of Vision Informatics, Osaka University Graduate School of Medicine
[3] Graduate School of Medical Sciences, Nagoya City University
[4] Milliman, Inc.
[5] Novartis Pharma K.K.

Corresponding author: Ryo Kawasaki
Division of Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, 2-2 Yamada-Oka, Suita, 565-0871 Osaka, Japan
E-mail: rkawasaki@pbhel.med.osaka-u.ac.jp

*These authors contributed equally to this work and are considered to be co-first authors of this manuscript.

Received: September 19, 2023
Accepted: December 28, 2023
J-STAGE Advance published date: January 26, 2024

No. 24007

INTRODUCTION

Chorioretinal vascular diseases (CRVDs), including neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and retinal vein occlusion (RVO), are leading causes of blindness in industrialized countries [1, 2]. Intravitreal pharmacotherapy has been developed and widely adopted for treating CRVDs and contributed to improving visual acuity and stabilizing the diseases [2].

Intravitreal anti-vascular endothelial growth factor (VEGF) therapy is currently considered the first-line treatment for CRVDs, and its treatment patterns vary depending on patient characteristics and each CRVD. Two anti-VEGF agents—ranibizumab, approved as a treatment for nAMD, RVO, and DME in 2009, 2013, and 2014, respectively, and aflibercept, approved as a treatment for nAMD, central RVO, branch RVO, and DME in 2012, 2013, 2015, and 2014, respectively—are widely used to treat CRVDs in Japan. As nAMD is a chronic progressive disease, it requires continuous and frequent anti-VEGF treatment. Various dosing regimens, including fixed and individualized regimens, have been used to reduce the treatment burden while maintaining treatment effects in clinical practice. DME and RVO occur in younger and older patients and have alternative treatment options to anti-VEGF, such as steroid and laser therapy, and a better prognosis. Despite such differences among CRVDs, recent patterns in anti-VEGF regimens have not been fully investigated in medical settings in Japan.

This study investigated the patterns of anti-VEGF treatment for CRVDs, treatment intervals, and the continuation and drop-out rates in recent years to advance the understanding of the current treatment status in Japan. When examining the treatment intervals, we focused on the maintenance phase, following the initiation phase with a loading dose of one injection per month. The prevalence of each type of CRVD in Japan was also estimated.

METHODS

STUDY DESIGN AND DATA SOURCE

This was a claims-based study using the health insurance claims database provided by the Medical Data Vision Co., Ltd. (Tokyo, Japan) from April 2008 to July 2018. The prevalence, anti-VEGF treatment (ranibizumab and/or aflibercept) intervals during the maintenance phase, and treatment continuation and drop-out rates for each type of CRVD (nAMD, DME, and RVO) were analyzed.

The database comprises data from acute care hospitals collated using the Japanese Diagnosis and Procedure Combination (DPC)/Per-Diem Payment System (DPC hospitals) [3]. It contains the information of approximately 20 million patients from 329 hospitals (approximately 19% of all DPC hospitals as of April 2018). It includes records of all diagnoses and medical procedures administered to both inpatients and outpatients in hospitals, regardless of age and insurance type. Records of diagnoses and medical procedures provided outside the hospitals were not included. The observation period for each patient was the duration between the first and last records of any medical procedure in the database.

NDB Open Data, a publicly available summary spreadsheet published by the Ministry of Health, Labour and Welfare (Third NDB Open Data: April 2016–March 2017) [4], was used to estimate the number of patients with CRVDs in Japan. This contained data on the prescription numbers for the 100 most-prescribed drugs in each therapeutic category and for each age and sex group over a 1-year period starting from April. The demographic data (as of October 1, 2016) were used to estimate the prevalence of CRVDs as the denominator [5].

This study was approved by the Clinical Research Promotion Network Japan on December 20, 2018 (CRTH258AJP02). As the database includes data collected for secondary use and was provided after anonymization, informed consent was not required according to ethical guidelines in Japan.

STUDY POPULATION

Patients having first nAMD diagnosis at an age ≥50 years, first DME diagnosis at an age ≥18 years, or first RVO diagnosis at an age ≥18 years during the observation period and without plural types of CRVD were included (**Supplementary Fig. 1**, **Supplementary Table 1** for the definition of each diagnosis). The diagnoses were defined based on the International Statistical Classification of Diseases and Related Health Problems, 10th revision [6]. The first diagnosis was defined as the earliest "FromDate" (recorded as the first diagnosis in the database) for each disease. To analyze the anti-VEGF treatment status, patients who received intravitreal anti-VEGF injections (ranibizumab and/or aflibercept) on the day of the first CRVD diagnosis or later were selected. Patients who were prescribed bevacizumab or pegaptanib during the observation period and those who received intravitreal anti-VEGF injections within a <22-day interval were excluded from the analyses.

OUTCOMES AND ANALYSES

We performed descriptive statistical analyses. To estimate the prevalence of each CRVD, the number of patients with each CRVD nationwide was estimated using the number of patients in the database, the ratio of the number of patients to the number of aflibercept injection records in the database, and the number of aflibercept injection records in NDB Open Data for each 5-year age group and for each sex. We assumed that the ratio of patients with each type of CRVD to the number of aflibercept injection records in the database was equal to the nationwide ratio. We calculated this ratio for all diagnosed patients, regardless of whether they were treated with aflibercept. Patients diagnosed with a CRVD (see **Supplementary Table 1** for the definition of each disease) from April 2016 to March 2017 were included. The number of aflibercept injections administered during the same period was also calculated. The prevalence was calculated in 5-year age groups and for each sex by dividing the estimated number of patients nationwide by that in the demographic data (see **Supplementary Fig. 2** for the estimation method).

The mean and median treatment intervals (days) during the maintenance phase of anti-VEGF treatment were calculated for each type of CRVD and for each patient group categorized according to the year of the first injection. The first injection was defined as the index injection, the date of the index injection was defined as the index date, and the year of the index date was defined as the index year. The treatment initiation phase was defined as the period with the index injection and injection(s) after the index within 22 to 37 days from the immediately preceding injection, with a maximum of 3, 5, or 1 injection(s) in total for nAMD, DME, or RVO, respectively. The maintenance phase was from the date of the last injection of the treatment initiation phase to the date of the latest injection in the database. The treatment interval was defined as the number of days between the date of the injection and the prior date of the next injection. If a treatment interval spanned to the next year, the entire interval was included in the year of the injection. **Supplementary Figs. 3** and **4** show these definitions.

The recent trend of the mean treatment interval during the maintenance phase of anti-VEGF treatment for each type of CRVD was examined (nAMD, 2009–2018; RVO, 2013–2018; and DME, 2014–2018). The mean treatment interval and distribution of patients were calculated according to the treatment year in each patient group (**Supplementary Figs. 3** and **4**). The patient groups were categorized according to the index and defined years of the treatment start in the database. The mean and quintile treatment intervals were determined by calculating the mean interval of maintenance injections for each patient and the mean among patient groups. The maximum, 75% quartile, median, 25% quartile, and minimum values of the treatment intervals were also calculated.

The treatment continuation and drop-out rates for anti-VEGF treatment for each type of CRVD and each 10-year age group were calculated. The Kaplan–Meier curve of the time from the administration of the index injection to the drop-out injection or the latest injection was plotted for each type of CRVD for each patient group, categorized according to the index year and age group. "Drop-out injection" was defined as the latest anti-VEGF injection after the index injection in cases where the patient did not receive the next anti-VEGF injection within 12 months before the end of the data period. If a patient had a data period of less than 12 months after the latest anti-VEGF injection, the latest injection was not considered a drop-out injection, but the data period of the patient was censored after the latest injection in the analysis of the treatment continuation rate. In addition to the continuation rate, we also used the drop-out rate as a measure to assess treatment continuation/discontinuation. The drop-out rate was calculated as the number of drop-out injections divided by the number of patients and was categorized according to the treatment year in the database. The treatment continuation could not be tracked in this database when a patient was transferred to another medical facility; therefore, the drop-out rate was defined as the rate of those who definitely dropped out of treatment, assuming that the patients with a data period of less than 12 months after the latest anti-VEGF injection continued the treatment. For the continuation rate, the coefficient of proportional hazards was calculated for each age group, each type of CRVD, and each calendar year since the treatment started.

SAS version 9.4 (SAS Institute, North Carolina, United States) was used for statistical analyses.

RESULTS

STUDY POPULATION

In the database, we identified 76,535, 49,704, and 37,681 patients with nAMD, DME, and RVO, respectively (**Supplementary Fig. 1**).

PREVALENCE OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION, DIABETIC MACULAR EDEMA, AND RETINAL VEIN OCCLUSION

Except in the 95–99-year age group, wherein the number of patients and aflibercept injections was small in the database, the peak ages of prevalence were 85–89 years for both sexes in the nAMD group; 70–74 and 75–79 years for men and women, respectively, in the DME group; and 80–84 and 85–89 years for men and women, respectively, in the RVO group (**Fig. 1a–1c**, **Supplementary Table 2**). Men had a higher prevalence of nAMD than women, except in the 95–99-year age group, and the difference tended to be larger in the older age groups than in other age groups. The prevalence of DME also tended to be higher in men than in women, and that of RVO was comparable between the sexes, except in the 95–99-year age group.

ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT INTERVALS DURING THE MAINTENANCE PHASE

The mean treatment interval ranges for each index year during the maintenance phase regarding anti-VEGF were approximately 94–100 and 89–100 days in the first and second years for nAMD, 111–120 and 129 days for DME, and 97–103 and 127 days for RVO, respectively, except for years with <100 patients and the two most recent index years, in which the entire year was not included (**Supplementary Table 3**). The median intervals tended to be shorter than the mean intervals (73–80, 98–102, and 87–93 days, respectively, in the first year) (**Fig. 2**, **Supplementary Table 3**). No notable tendency was observed over the years regarding all CRVDs.

DME was associated with a longer mean treatment interval in all age groups compared to nAMD and RVO (**Supplementary Table 4**). A longer treatment interval was observed in the 70s and 80s age groups than in other age groups for RVO; however, no difference was observed among the age groups for nAMD and DME.

No difference was observed between the treatment patterns for nAMD using ranibizumab and aflibercept, whereas longer treatment intervals were noted for RVO and DME using aflibercept (**Supplementary Fig. 5**, **Supplementary Table 5**).

CONTINUATION/DROP-OUT RATES IN ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT

The treatment continuation rate for all CRVDs tended to increase in the later index years (**Supplementary Fig. 6**).

For nAMD, the treatment continuation rate tended to be lower in the 50s and 60s age groups than in the 70s and 80s age groups. For RVO, the treatment continuation rate was lower in the 40s–60s age group than in the 70s and 80s age groups (**Supplementary Table 6**).

The drop-out rate in the index year tended to decrease over the years for all CRVDs. The drop-out rate decreased from 63% to 32% from 2009 to 2016 for nAMD, from 69% to 53% from 2014 to 2016 for DME, and from 47% to 36% from 2013 to 2016 for RVO (**Table 1**). After the first injection, the drop-out rate increased from approximately 10% to 15% and then 17% in 2012, 2014, and 2015, respectively, for nAMD. It slightly decreased from 48% to 43% from 2014 to 2016 for DME and remained stable at approximately 30% for RVO.

DISCUSSION

Using a Japanese claims database, we investigated the patterns of anti-VEGF treatment intervals in the maintenance phase, treatment continuation, and drop-out rates for nAMD, DME, and RVO. We also estimated the prevalence of each type of CRVD in Japan. To the best of our knowledge, this is the first study to describe the nationwide treatment patterns and prevalence of these diseases in a real-world setting in Japan.

Except for the 95–99-year age group, the prevalences of nAMD and RVO were the highest in the 80s age group, whereas that of DME was the highest in the 70s age group. The prevalences of nAMD and DME were higher in men than in women, whereas regarding RVO, it was similar for both sexes. A previous community-based study showed that the prevalence of late AMD (exudative AMD and geographic atrophy) tended to increase with age and was higher in men than in women [7, 8]. A Korean study reported that the peak prevalences of exudative AMD in men and women were in the 80–84- and 75–79-year age groups, respectively [9]. An RVO prevalence of 0.52% [10] or 0.77% [11] has been reported, with an increase with age by the 80s and no significant difference between the sexes [10, 11]. Our results are comparable with these previous findings.

Regarding the anti-VEGF treatment intervals in the first and second years of the maintenance phase, the mean treatment intervals for all CRVDs were 10–20 days longer than the median intervals. Although a change reflecting the acceptance of regimens and the available treatment options was expected, no notable tendency was observed in the treatment intervals in the first year for all CRVD types categorized according to the index year. A US study also reported no change in the injection frequency in the first year of anti-VEGF treatment for

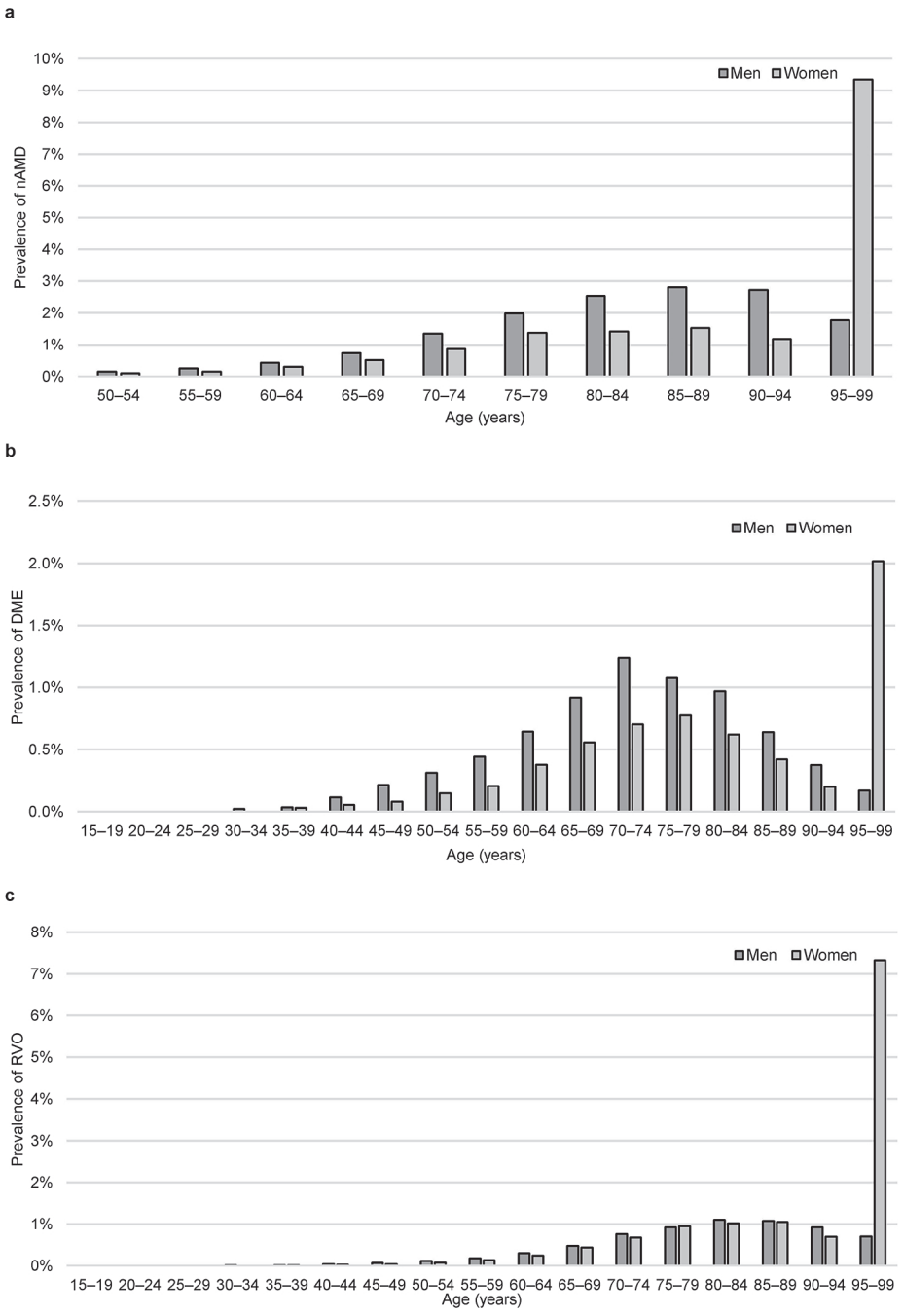

Fig. 1 **Prevalences of nAMD, DME, and RVO by age–sex group**

The prevalence of (a) nAMD, (b) DME, and (c) RVO by age–sex group (April 2016–March 2017).
DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration; RVO, retinal vein occlusion

patients with DME over 2013–2018 [12]. Meanwhile, a Japanese study examined the number of anti-VEGF injections in patients with DME 2 years from treatment initiation, starting between 2010 and 2015, and a significant increasing trend was observed [13]. The shorter treatment interval and exclusion of the period before the maintenance phase in our study may contribute to these different results.

DME was associated with the longest treatment interval in the first year among the CRVDs. The median treatment interval for all CRVDs tended to be longer in the second year from the 2013 index year and for each type

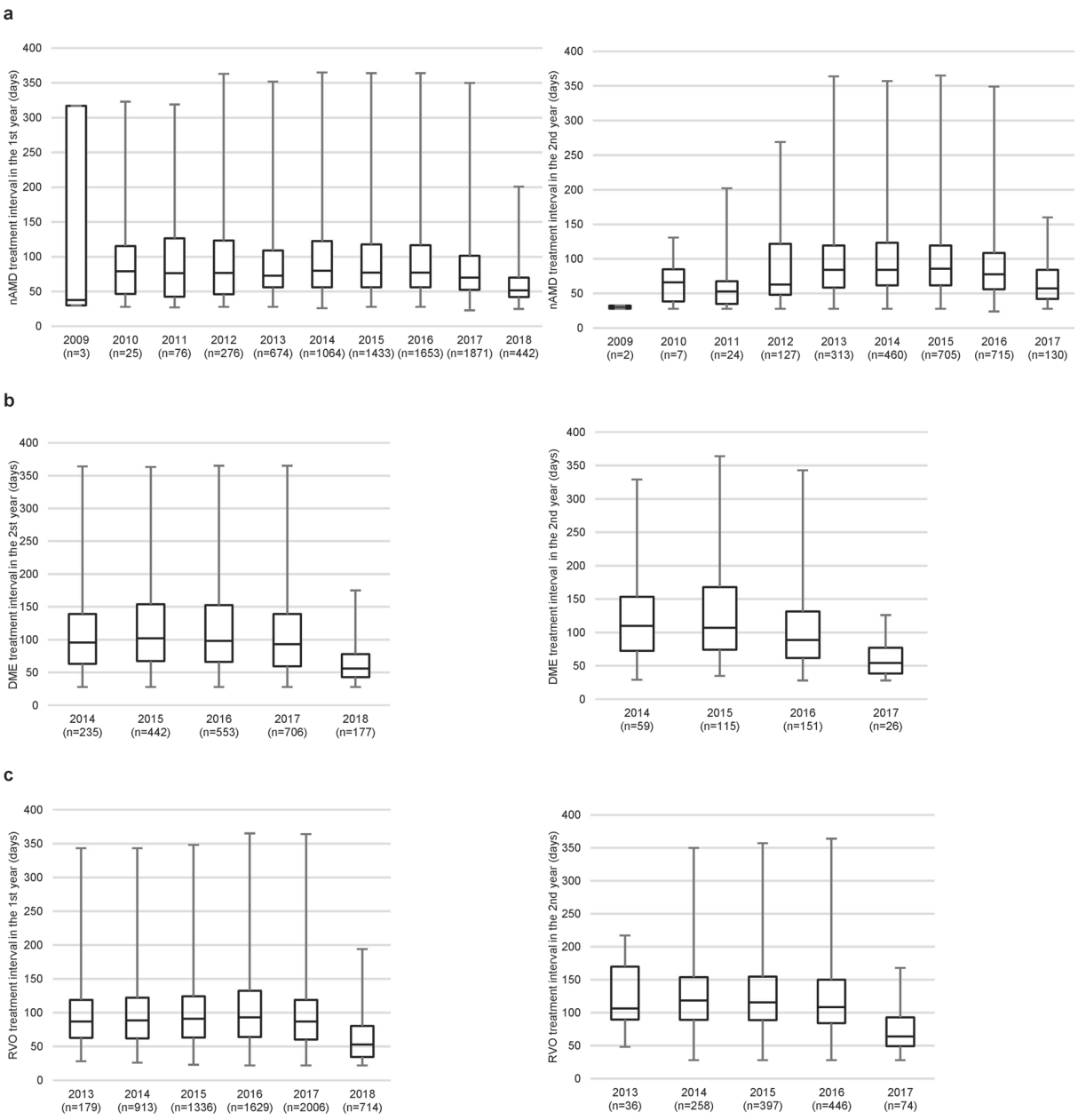

Fig. 2 **Anti-VEGF treatment intervals in the first and second years of the maintenance phase by index year**

Box plots indicate the maximum, 75% quartile, median, 25% quartile, and minimum values of the treatment interval for (a) nAMD, (b) DME, and RVO (c) in the first (left column) and second (right column) years of the maintenance phase.
DME, diabetic macular edema; N, number; nAMD, neovascular age-related macular degeneration; RVO, retinal vein occlusion

of drug. Based on clinical experience, we assumed that a longer treatment interval for DME might be due to the concomitant administration of therapies, such as steroid and laser therapy. The increase in the treatment interval in the second year suggests that treatment is generally administered more intensely in the first year. Future studies are necessary to verify this assumption. In the analysis performed according to the types of CRVDs, the median treatment intervals for DME and RVO were longer than that for nAMD. This may be associated with differences in disease and patient characteristics among those with CRVDs. As most patients with nAMD are older, they can dedicate more time to treatment and have lower out-of-pocket medical costs than younger patients and are, therefore, more likely to seek medical treatment. Additionally, a treat-and-extend regimen—a proactive approach

Table 1 Drop-out rate of the anti-VEGF treatment

CRVD	Calendar year starting the treatment	Number of patients	Drop-out in the 1 year after starting the treatment (%)	Drop-out after the first injection (%)
nAMD	2009	8	63%	N/A
	2010	50	52%	N/A
	2011	170	55%	9%
	2012	478	49%	10%
	2013	1087	47%	13%
	2014	1753	47%	15%
	2015	2311	42%	17%
	2016	2596	32%	16%
	2017	3076	8%	N/A
	2018 (until July)	1725	0%	N/A
DME	2014	555	69%	48%
	2015	978	62%	45%
	2016	1136	53%	43%
	2017	1387	15%	N/A
	2018 (until July)	868	0%	N/A
RVO	2013	269	47%	32%
	2014	1416	46%	35%
	2015	1923	43%	30%
	2016	2356	36%	31%
	2017	2888	8%	N/A
	2018 (until July)	1697	0%	N/A

Abbreviations: CRVD, chorioretinal vascular diseases; nAMD, neovascular age-related macular degeneration; DME, diabetic macular edema; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor; N/A, not available

in which patients receive treatment at every predetermined hospital visit—is reportedly more frequently used in nAMD [14], and drastic vision loss due to inadequate treatment is more likely to occur in nAMD than in DME. The reactive pro-re-nata regimen is commonly used in DME [15], and the same may be true in RVO. This may contribute to the longer intervals observed.

The mean and median treatment intervals in the first year for nAMD in the present study, approximately 95 and 77 days, respectively, are longer than those observed in previous US studies [16, 17]. This may be due to differences in medical insurance systems, clinical entities of nAMD, and treatment responses of patients in different countries and races. The treatment interval in the first year was also longer for DME (approximately 115 days on average) in our study than that in a Belgian study [18]. The previous study also observed the treatment interval from the first injection, whereas our study excluded injections before the maintenance period. The difference may be related to the different intervals between studies. Further, a decrease in treatment frequency over time was also reported, which seems consistent with our study, where an increasing tendency in the treatment intervals from the first to the second year was observed.

The treatment continuation rate in the first year of treatment for all CRVDs increased over the years. A tendency of decreasing drop-out rates in the index year, stratified according to the calendar year, was also observed. Possibly, confidence in the anti-VEGF treatment and the acceptance of the treatment by both physicians and patients have improved. Further studies are necessary to determine whether confidence in anti-VEGF treatment for each CRVD has improved. The current availability of brolucizumab (approved in 2020) and faricimab (approved in 2022) for nAMD and DME may

affect the treatment trend, which was after the data range of this study. Finally, coronavirus disease 19 may have further changed the treatment trend for CRVDs in and after 2019 by refraining from regular clinic visits.

The treatment continuation and drop-out rates in the first year of treatment for nAMD observed in the present study align with those of previous studies. Previous retrospective studies have indicated that, in clinical practice, treatment termination occurs in approximately 30–60% of patients in the first year of treatment [19–22]. In a Japanese study with a mean follow-up period of 12.8 ± 3.6 months (minimum, 6 months; maximum, 20 months), 20.7% of the patients dropped out between 2008 and 2010 [23].

LIMITATIONS

First, the claims database used in this study does not include data other than those from DPC hospitals; thus, data on treatments in other settings and after changes in settings could not be obtained from the database. Second, diagnoses and treatments were defined based on the claims data. Consequently, the accuracy of the records affects the accuracy of diagnoses and treatments. Third, the database does not contain information on whether only one or both eyes were treated. Thus, the 21-day injection interval was used as a proxy definition of bilateral treatment; if two consecutive claims associated with intravitreal anti-VEGF injections administered within <21 days were noted, the patient's data were excluded from the study. This may have contributed to the lengthening of the mean treatment interval compared to those in previous studies. However, if a patient who underwent bilateral treatment received anti-VEGF injections for one eye each time with a ≥21-day interval from one eye to the other eye, they were included and the interval from one eye to the other eye was determined as that for one eye. This made the interval shorter than the actual one. Fourth, as the database does not include visual acuity outcomes, we could not determine whether some treatment patterns, including long intervals and termination of treatment, were due to the improvement in visual acuity. Notably, drop-out occurs both in cases where symptoms are alleviated and in cases where symptoms are exacerbated. We could not differentiate this as no clinical outcomes (e.g., retinal imaging data or visual acuity) were available. In addition, if well-controlled patients treated on the basis of the pro-re-nata regimen did not require a subsequent anti-VEGF treatment for ≥12 months, they were misclassified as drop-out, even though they were still followed up by physicians. Therefore, an increase in the popularity of treat-and-extend regimen itself, rather than the effect of the regimen, may contribute to an increase in the continuation rate and a decrease in the drop-out rate in this study. Finally, although we used large nationwide databases, there may be limitations in the generalizability of the study findings. As the claims database included data from large DPC hospitals, the possibility that the dataset mostly contained data on severe disease statuses and/or comorbidities may be higher than that of the general Japanese patient population.

CONCLUSIONS

This study illustrated the patterns of anti-VEGF treatment for nAMD, DME, and RVO in Japan. Regarding all CRVDs, the anti-VEGF treatment intervals during the maintenance phase did not change significantly over the years. Although the treatment continuation and drop-out rates after the first treatment for all CRVDs differ among the age groups, the treatment continuation rate has improved in recent years. We believe that this study provides information that advances the understanding of the treatment patterns for CRVDs in clinical settings in Japan.

CONFLICTS OF INTEREST

Fumi Gomi (FG) and Ryo Kawasaki (RK) report receiving honoraria for advisory board participation from Novartis Pharma K.K. for the current work. FG reports receiving grant support from Santen, lecture fees from Bayer, Senju, Chugai, Santen, and Novartis, and honoraria for advisory board participation from Senju, Kyowa Kirin, and Boehringer Ingelheim; and serves as a director of the Japanese Ophthalmological Society, Japanese Retina and Vitreous Society, and Japanese Ocular Circulation Society, outside the submitted work. RK belonged to an endowed department funded by Topcon until February 2023; reports receiving research funding from Senju, Nanolux, Tamron, and WHILL, consulting fees from Office Future and Nanolux, and honoraria for lectures from Novartis, Bayer, Kowa, Alcon Japan, and Bausch Lomb; and serves as a delegate member of the Japan Epidemiological Association, a councilor member of the Japanese Society of Cardiovascular Disease Prevention and Japanese Society of Artificial Intelligence in Ophthalmology, an assistant secretary-general of the Asia-Pacific Tele-ophthalmology Society, and a research standing committee member of the Asian Pacific Academy of Ophthalmology, outside the submitted work. Yuichiro Ogura reports receiving grant supports from Boehringer Ingelheim and Novartis, personal fees from Bayer, Novartis, Hoya, Kowa, Alcon, Kyoto Drug Discovery & Development, Senju, Iveric Bio,

Apellis Pharmaceutical, Chengdu Kanghong Biotechnology, and Chugai, lecture fees from Bayer, Novartis, Santen, Senju, Sanwa Kagaku, Wakamoto, Otsuka, Topcon, and Nikon, and fee for employment from Genentech; and serves as an executive director of the Japanese Ophthalmological Society, the president of the Japanese Retina and Vitreous Society, a director of the Japanese Society of Ophthalmic Diabetology, Japanese Society for Ocular Circulation, Japanese Society for Microcirculation, and Japanese Society for Ocular Pharmacology, and a board member of the Euretina (European Society of Retina Specialist) and Retina World Congress, outside the submitted work. Masaumi Yamabe and Kota Imai are employees of Novartis Pharma K.K., Japan. Kosuke Iwasaki and Tomomi Takeshima are employees of Milliman Inc., which received funding from Novartis Pharma K.K. to perform the analyses and develop the manuscript.

ACKNOWLEDGMENTS

This study was funded by Novartis Pharma K.K., Japan. We would like to thank Editage (www.editage.com) for the English language editing, which was funded by Novartis Pharma K.K., Japan.

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