

Effectiveness of Current Treatments for Wet Age-Related Macular Degeneration in Japan: A Systematic Review and Pooled Data Analysis

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Purpose: We conducted a systematic review to investigate the effectiveness of clinical treatments for wet age-related macular degeneration (wAMD) in Japanese patients in the decade since anti-vascular endothelial growth factor (VEGF) therapies were introduced.

Methods: PubMed was searched for articles published in English between 1 January 2008 and 30 September 2018 using a multistring search strategy. Reviews were scanned for additional relevant studies and select gray literature was evaluated. Mean and/or median for the logarithm of the minimum angle of resolution (logMAR) visual acuity (VA), central retinal thickness (CRT), and the number of injections after 12 months of treatment were calculated using extracted data. Data were stratified by disease type and treatment modality.

Results: Of 335 studies identified, 94 were selected for data extraction (147 treatment arms; typical AMD, n = 25; polypoidal choroidal vasculopathy [PCV], n = 85). Mean (median) logMAR VA was 0.44 (0.32) for typical AMD and 0.34 (0.31) for PCV; the respective mean number of anti-VEGF injections was 5.6 and 4.6. The mean CRT was approximately 220 μ m for both groups. For typical AMD, anti-VEGF monotherapy resulted in better VA outcomes than photodynamic therapy (PDT) alone. For PCV, anti-VEGF monotherapy or anti-VEGF plus PDT combination therapy resulted in better VA and CRT outcomes than PDT monotherapy. Combination therapy required fewer injections than anti-VEGF monotherapy (PCV, 3.2 versus 5.3).

Conclusion: wAMD treatment has advanced dramatically in the years since anti-VEGF drugs were introduced in Japan. Discrete patient populations may benefit from differing management regimens, including the fewer injections required with combination therapy.

Keywords: visual acuity, polypoidal choroidal vasculopathy, anti-vascular endothelial growth factor therapy, photodynamic therapy

Introduction

Globally, age-related macular degeneration (AMD) is the third leading cause of blindness following cataracts and glaucoma¹ and is the primary cause of blindness in industrialized countries.² AMD results from changes in the macular region of the retina in older people (aged >55 years), affecting photoreceptors and the retinal pigment epithelium, leading to a progressive loss of vision.³ The incidence of AMD is increasing as the global population ages,^{4,5} and management of age-related diseases over the coming decades is of particular concern in countries with a large proportion of elderly citizens, such as Japan. Population-based cohort studies in Japan have indicated that the overall prevalence of AMD ranges from 13.4%⁶ to 21.5%,⁷ with a notable increase between the ages of 50–59 years (16.4%) and 70–74 years (32.2%).⁸ Furthermore, the number of Japanese patients with AMD is expected to increase over the next 1–2 decades, potentially peaking in 2035.⁹

Wet AMD (wAMD), also known as exudative or neovascular AMD, develops in about 10% of all AMD cases¹⁰ and arises due to blood vessels from the choroid growing into the normally avascular retinal pigment epithelium and sub-retinal regions.¹¹ wAMD is an infrequent complication of AMD, with an estimated global prevalence rate of 0.46%.⁴ However, wAMD accounts for 80–90% of the severe vision loss associated with AMD.¹² Furthermore, one phenotype of wAMD called polypoidal choroidal vasculopathy (PCV) is known to occur at a higher prevalence in Japanese and Asian individuals than Caucasians.^{13–15} Patients with wAMD rapidly lose the central vision required for tasks such as reading, screen use, and driving,¹⁶ thus restricting both leisure activities and the ability to work, and severely reducing quality of life.^{16–18} The economic burden caused by visual impairment is substantial, in Japan; in 2007, it was estimated to be about 8785 billion yen, which equated to 1.7% of the gross domestic product in that year.¹⁹

The treatment algorithm for wAMD in Japan is driven by disease severity, and the recommended standard-of-care is anti-vascular endothelial growth factor (anti-VEGF) therapy.²⁰ This class of drug binds to excess VEGF protein that would otherwise promote the erroneous growth of new blood vessels.²¹ As this protein is also essential for normal tissue healing and growth, VEGF must be only suppressed in the eye; therefore, these drugs are administered via intraocular injections on an intermittent or *pro re nata* (PRN) schedule.²¹ Anti-VEGF inhibitors first became available in Japan in 2008,²² and drugs in this class now approved in Japan include the monoclonal antibody ranibizumab and the synthetic protein aflibercept, both of which have proven clinical effectiveness in wAMD.^{23–27} To treat wAMD in Japan, anti-VEGF drugs are used either as monotherapy or in combination with photodynamic therapy (PDT).²⁰

Drug development for wAMD is ongoing,^{28–30} and as new therapies become available, it is vital that Japanese patients and clinicians have the necessary information to assess management options critically. This, in turn, will allow them to make optimal treatment decisions. Thus, the primary objective of this study was to systematically review randomized controlled trials, observational studies, case studies, and treatment guidelines to investigate the effectiveness of clinical treatments for wAMD in Japanese patients in the decade following the 2008 introduction of anti-VEGF therapies.

Methods

Data Sources and Search Methodology

The methodology used for this systematic review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines³¹ ([S1 Text](#)) and documentation from the National Institute for Health and Clinical Excellence in the United Kingdom.³² The protocol was not registered. A comprehensive search was conducted in PubMed for articles published in English between 1 January 2008 and 30 September 2018. A multistring search strategy was implemented, and either title/abstract (TIAB) or medical subject heading (MeSH) entries were searched ([S2 Text](#)).

Study Selection Criteria

In the first round of screening, titles and abstracts of all records retrieved from the literature search were reviewed by YS and William YuanHao Kuan (Syneos Health, Tokyo, Japan). The relevance of each article was evaluated based on the inclusion and exclusion criteria ([Table 1](#)). A Population, Intervention, Comparison, and Outcome strategy was used to construct the specific research question. The AMD diagnostic criteria specified were those published by the Japanese Ministry of Health, Labour and Welfare.³³ Studies of patients with retinal angiomatous proliferation were excluded, as this is a unique type of wAMD. Additional inclusion and exclusion criteria included the type of article, sample size, and geographic setting. Citations that did not match the eligibility criteria and duplicate citations were excluded. Unclear citations were included for more detailed evaluation. Any disparities were resolved by discussion between all authors. After reaching a consensus, the full text of studies identified as potentially relevant was reviewed in a second screening round and included in the analyses if the studies fulfilled the specified criteria.

Data Extraction

The data presented in the selected studies were extracted by William YuanHao Kuan (Syneos Health), and the quality was checked by YS. The extracted information included type of study or article, number of sites, study duration, number

Table I Inclusion and Exclusion Criteria for the First Round of Literature Evaluation

Item	Inclusion	Exclusion
PICO strategy		
Patient population	Japanese patients aged ≥ 50 years with choroidal neovascularization who meet Japanese wAMD diagnostic criteria ²⁹	Patients with central serous chorioretinopathy, lesions from myopia, and other ocular diseases causing vision impairment, including inflammatory and degenerative diseases
Intervention/comparator	Any approved, widely-used, or guideline-recommended interventional therapy in Japan ^{3,19}	Studies not reporting any of the listed interventions/comparators of interest
Outcomes	Reporting of VA, central retinal thickness, and/or number of injections at 12 months	Studies not reporting outcomes of interest
Other criteria		
Article type	RCT, observational study, case series, conference proceeding, current wAMD diagnosis/treatment guidelines	Non-systematically conducted reviews or editorials
Sample size	≥ 10 Japanese patients with a diagnosis of wAMD	< 10 patients
Geographic setting	Japan	Any other country

Notes: *Includes anti-VEGF alone, anti-VEGF plus photodynamic therapy, photodynamic therapy alone, and other approved treatments.

Abbreviations: PICO, Population, Intervention, Comparison, and Outcome; RCT, randomized controlled trial; VA, visual acuity; VEGF, vascular endothelial growth factor; wAMD, wet age-related macular degeneration.

of patients, baseline demographic and clinical characteristics, type of wAMD, risk factors, details of diagnosis and management, and clinical efficacy endpoints after 1 year of treatment (including visual acuity [VA], central retinal thickness [CRT], and number of injections [if applicable]). For dichotomous outcomes, the number of patients analyzed (N) and the number of patients with the outcome (n) were extracted. For continuous outcomes, N, mean, median, and interquartile range (IQR) were recorded.

Statistical Methods

Data from all relevant studies were pooled to report mean and/or median (IQR) for the logarithm of the minimum angle of resolution (logMAR) VA, CRT, and the number of injections. Data were stratified by type of wAMD and/or type of treatment. To explore the clinical efficacy endpoints stratified by these factors, Box and Whisker plots were created (indicating the median, 25th, and 75th percentile values). No adjustment was made for the data quantity (number of articles/treatment arms) or variations in baseline parameters. Data reported using the Early Treatment Diabetic Retinopathy Study scale was not converted into logMAR. As we did not adjust the data weighting of the papers included in the analysis, no tests for statistical difference were conducted. Microsoft Excel 2016 was used for all calculations.

Results

Article Selection

A PRISMA flowchart of the identification process is shown in [Figure 1](#). The initial search identified 335 studies. After removing duplicates and those articles that did not meet the eligibility criteria, 280 articles remained for the detailed second-round assessment. An additional 17 gray literature articles were also subjected to detailed evaluation. Articles were excluded based on the patient population and study design, then by intervention, and finally by outcome. Following the full-text evaluation, 94 articles were selected for data extraction, resulting in a total of 147 individual treatment arms with available data. A full list of the 94 selected articles is provided as [S1 Table](#).

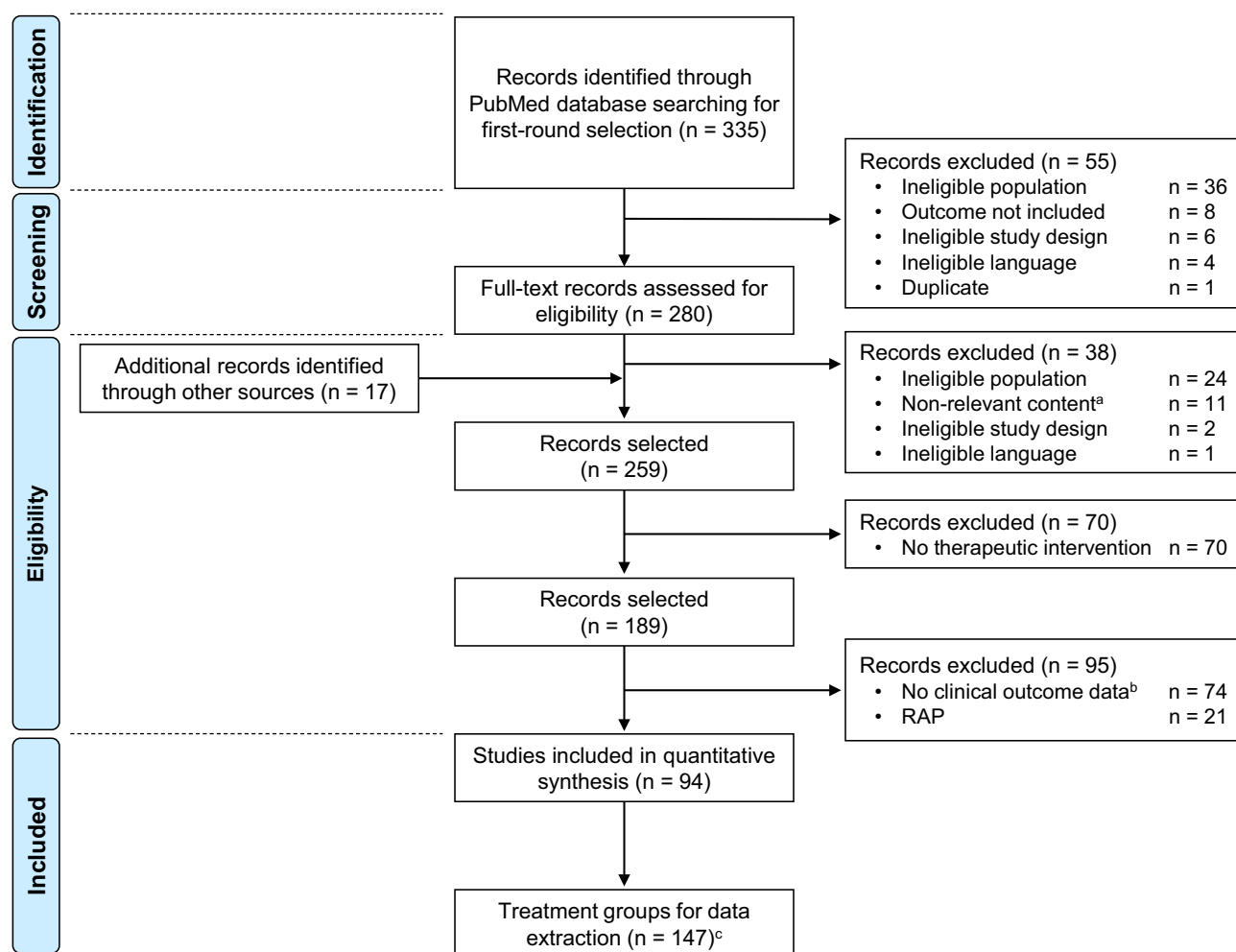


Figure 1 PRISMA flow diagram. ^aIncludes articles reporting epidemiology, treatment methodology, quality of life, and economic analyses. ^bNo data on VA or number of injections after 12 months of treatment. ^cTotal number of individual treatment arms for which data were reported.

Abbreviations: PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RAP, retinal angiomatous proliferation; VA, visual acuity.

Stratification Factors

A breakdown of the disease types and treatment modalities in the 147 treatment groups is shown in Table 2. More treatment arms included patients with PCV (n = 85) than with typical AMD (n = 25). The two main types of treatments for wAMD were anti-VEGF injections (generally intravitreal aflibercept or intravitreal ranibizumab) and PDT, either as

Table 2 Breakdown of Data Stratification Factors of the 147 Evaluable Treatment Groups

		Treatment Modality				Total
		Anti-VEGF	Anti-VEGF + PDT	PDT	Other ^a	
Type of wAMD	Typical AMD	20	1	3	1	25
	PCV	40	23	19	3	85
	Other ^b	24	2	5	6	37
	Total	84	26	27	10	147

Notes: ^aIncludes treatment with steroids or pegaptanib. ^bDisease type that cannot be classified as typical AMD or PCV.

Abbreviations: AMD, age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; PDT, photodynamic therapy; VEGF, vascular endothelial growth factor; wAMD, wet AMD.

monotherapy or in combination. Interventions such as bevacizumab, pegaptanib, brolucizumab, and triamcinolone acetonide were rarely reported. A visualization of the treatment arms included in each outcome calculation is shown as [S1 Figure](#). Outcomes for other types of wAMD were not calculated, as they were defined as neither typical AMD nor PCV. Additionally, outcomes were not calculated for other types of treatment because they included off-label steroid treatment and pegaptanib, which is rarely used in clinical practice.

Outcomes

Data for VA after 12 months of treatment, stratified by disease type, are shown in [Figure 2A](#). The mean (median) logMAR VA after 12 months of treatment was 0.44 (0.32) for typical AMD and 0.34 (0.31) for PCV.

Data for VA after 12 months of treatment, stratified by disease type and treatment modality, are shown in [Figure 2B–C](#). For typical AMD, VA after 12 months of treatment tended to be better with anti-VEGF monotherapy than with PDT monotherapy. For PCV, post-treatment VA tended to be better with anti-VEGF monotherapy or with anti-VEGF plus PDT combination therapy than with PDT monotherapy.

Data for CRT after 12 months of treatment, stratified by disease type, are shown in [Figure 2D](#). No notable difference between disease type was observed; in both groups, the mean CRT after 12 months was approximately 220 μm .

Data for CRT after 12 months of treatment, stratified by disease type and treatment modality, are shown in [Figure 2E](#). Among the 13 typical AMD studies, anti-VEGF agents were the predominant treatment. Patients received either anti-VEGF monotherapy (12 studies) or anti-VEGF plus PDT (1 study); there were no studies in which patients were treated with PDT monotherapy. Therefore, we considered that stratification of the typical AMD group would not provide meaningful data; as a result, only data for the PCV group were stratified and evaluated. Anti-VEGF monotherapy and anti-VEGF plus PDT combination therapy resulted in lower mean CRT (ie, an improvement) after 12 months compared with PDT monotherapy.

Data for the number of anti-VEGF injections during the first 12 months of treatment, stratified by disease type, are shown in [Figure 2F](#). The mean number of anti-VEGF injections during the first 12 months of treatment tended to be lower for patients with PCV (4.6) than those with typical AMD (5.6).

Corresponding data stratified by both disease type and treatment modality are shown in [S2 Figure](#) and [Figure 2G](#). For patients with PCV, the mean number of anti-VEGF injections during the first 12 months of treatment was lower when receiving anti-VEGF plus PDT combination therapy (3.2) than anti-VEGF monotherapy (5.3).

When outcomes were calculated using only the treatment arms for which all outcome data were available (VA, CRT, and injection number), no differences were observed in the results (data not shown).

Discussion

In the decade since the introduction of anti-VEGF drugs for Japanese patients with wAMD, 94 studies including clinical effectiveness measures (VA, CRT, and injection number) have been published, totaling 147 individually evaluable treatment arms. Among Japanese patients with wAMD, more studies evaluated treatment for PCV than typical AMD. Previous studies have suggested that PCV occurs at a higher rate in Japanese/Asian individuals than Caucasians,^{13–15} and that PCV is a relevant problem in Japan;³⁴ hence, there is likely to be clinical interest in evaluating treatments for AMD in Japanese populations. Overall, the most common treatments for AMD were anti-VEGF drugs and PDT, either as monotherapy or in combination, which is in line with current recommendations both in Japan and globally^{20,35–37} where anti-VEGF therapy is the current standard-of-care.

The production of high-quality systematic reviews can provide a strong evidence base to underpin clinical care.³⁸ The use of this methodology to evaluate wAMD treatment in Japan allowed us to assess a large body of pooled evidence on clinical outcomes and observe whether effectiveness aligns with current practice recommendations. The pooled analysis of efficacy outcomes in patients with typical AMD indicated that anti-VEGF monotherapy yielded better results than PDT monotherapy in terms of VA after 12 months of treatment. However, baseline values varied between treatment groups because of the different studies that were included in our analyses. Both anti-VEGF monotherapy and anti-VEGF plus PDT combination therapy yielded better results in terms of VA and CRT for patients with PCV than PDT monotherapy after 12 months of treatment. Moreover, anti-VEGF plus PDT combination therapy required fewer

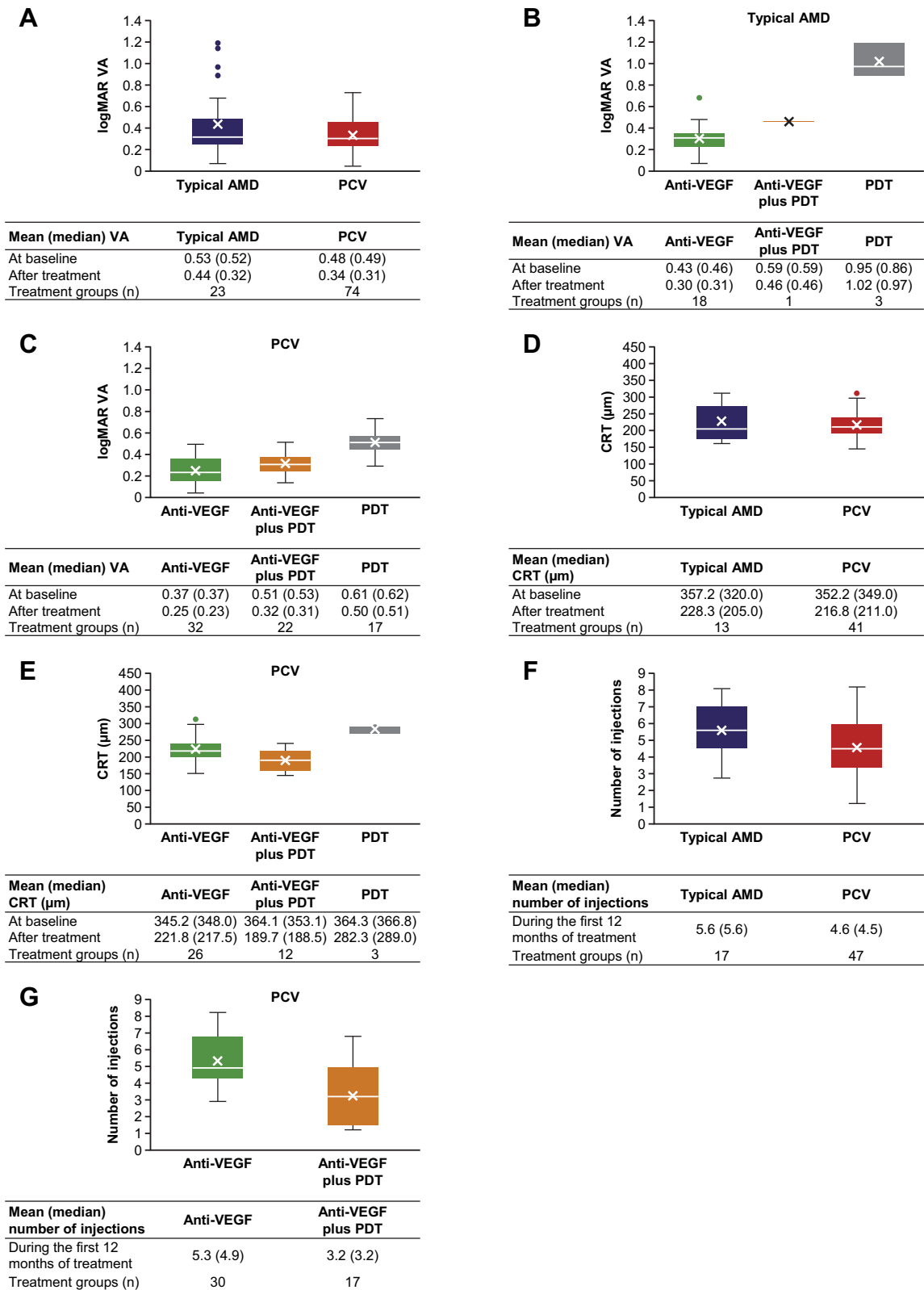


Figure 2 Outcomes after 12 months of treatment: (A) VA stratified by disease type; (B) VA stratified by disease type (typical AMD) and treatment modality; (C) VA stratified by disease type (PCV) and treatment modality; (D) CRT stratified by disease type; (E) CRT stratified by disease type (PCV) and treatment modality; (F) Number of anti-VEGF injections stratified by disease type; and (G) Number of anti-VEGF injections stratified by disease type (PCV) and treatment modality; baseline values vary by treatment group.

Abbreviations: AMD, age-related macular degeneration; CRT, central retinal thickness; logMAR, logarithm of the minimum angle of resolution; PCV, polypoidal choroidal vasculopathy; PDT, photodynamic therapy; VA, visual acuity; VEGF, vascular endothelial growth factor.

injections than anti-VEGF monotherapy. The reduction in injection number is of particular interest to patients and clinicians. Intraocular injections require specialist expertise and can be labor-intensive and costly.³⁹ Furthermore, many patients experience a psychosocial and practical burden from the treatment schedule.^{18,40,41} As a result, patients with wAMD in real-world practice are often undertreated, resulting in a lack of improvement (or even deterioration) in VA over time.^{42,43} Because of the highly invasive nature of treatment and the burdens associated with the treatment schedule, reduced dosing is desirable regardless of whether combination treatment or anti-VEGF monotherapy is used. As newer anti-VEGF agents are launched,⁴⁴ it is hoped that treatments requiring fewer injections will become available.

It is clear from our study findings that progress has been made in the treatment of wAMD in the years since the introduction of anti-VEGF therapy in Japan. However, there remains a need for novel treatments and regimens that offer a better prognosis for VA while requiring fewer injections.³⁹ Many recent studies have evaluated PRN, quarterly, and “treat and extend” dosing regimens instead of fixed dosing in an attempt to balance VA improvement and maintenance with fewer injections.⁴⁵ The anti-VEGF antibody fragment brotacizumab, which is now approved in several countries including the United States and Japan,⁴⁶ can be used with a 12-weekly maintenance schedule.⁴⁷ In addition to the possibility of treatment with fewer doses, brotacizumab has excellent fluid control.⁴⁸ There is also interest in sustained-release delivery devices for both novel and approved agents,^{49–52} in oral anti-VEGF formulations,^{53,54} and in gene therapy.^{55,56} The diversity of subject areas covered in wAMD research within an elderly Japanese population was narrow, with some search terms returning little evidence. Treatment comparisons may have suffered from heterogeneity in the study design and procedures, and no statistical comparisons were conducted.

Conclusions

The findings outlined in this study represent a large body of evidence relating to wAMD treatment and treatment outcomes in Japan. During the decade since the introduction of anti-VEGF drugs in Japan, wAMD treatment has advanced dramatically. The present results appear to confirm the treatment outcomes observed in clinical practice and suggest that discrete patient populations may gain optimal benefits from differing management regimens. Nevertheless, the development of new drugs and treatment regimens that offer an improved prognosis for VA and require fewer injections remains an important unmet clinical need.

Abbreviations

AMD, age-related macular degeneration; CRT, central retinal thickness; IQR, interquartile range; logMAR, logarithm of the minimum angle of resolution; MeSH, medical subject heading; PCV, polypoidal choroidal vasculopathy; PDT, photodynamic therapy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRN, *pro re nata*; TIAB, title/abstract; VA, visual acuity; VEGF, vascular endothelial growth factor; wAMD, wet AMD.

Data Sharing Statement

All data supporting the results are included in the manuscript.

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Disclosure

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