Patient Preference and Adherence

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REVIEW

Patient Preference on Age-Related Macular Degeneration Treatment: A Systematic Review

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Purpose: Patient preference is important in decision-making processes, such as drug approval and price determination. We conducted a systematic review regarding the preference of age-related macular degeneration (AMD) treatment.

Patients and Methods: We searched for articles on patient preferences for AMD treatment published between January 1, 2000 and December 31, 2023 using EMBASE, Google scholar, MEDLINE, and PLOS.

Results: Seven studies were included in this systematic review. Conjoint analysis was used in all seven trials, of which six were Discrete Choice Experiments and one was a ranking. These studies were conducted in Germany, United States, United Kingdom, Japan, Spain, and Singapore. Six studies focused on patients with neovascular AMD (nAMD, also called wet AMD, ie, wAMD), and one focused on patients with nAMD or diabetic macular edema. The attributes of the treatments used in these seven studies were efficacy, safety, convenience, and cost. Overall, the relative importance of attributes related to efficacy and safety were the highest, followed by those related to convenience and costs. The convenience and cost attributes were almost equal.

Conclusion: Although the definitions of treatment attributes differed among the studies, patients with nAMD considered efficacy and safety to be the most important. The results of several studies suggest that patient preferences may be affected by patient demographics, such as sex. Although there are currently only a few preference studies on patients with AMD, it is necessary to continue conducting studies to understand the trends in patient preferences according to patient demographics.

Keywords: patient preference, nAMD, systematic review, discrete choice experiment

Introduction

Age-related macular degeneration (AMD) affects the macular region of the retina and leads to the loss of central vision. AMD is classified into early and late AMD; the latter includes neovascular age-related macular degeneration (nAMD) and dry age-related degeneration. Late AMD has a profound impact on the quality of life and functional independence, as it leads to loss of central visual acuity, severe and permanent visual impairment, and legal blindness.[1–3] Of these, nAMD, which affects approximately 200 million people worldwide, is a major cause of vision loss in people aged >60 years and is expected to increase the number of patients owing to the global aging of the population, making it a public health issue with a significant socioeconomic impact.[4–6]

According to the Japanese guidelines for the treatment of AMD[7] during the study period, anti-vascular endothelial growth factor (anti-VEGF) agents were recommended for typical AMD; photodynamic therapy (PDT), anti-VEGF agents, and their combination therapy for polypoidal choroidal vasculopathy; and PDT and anti-VEGF agent combination therapy for retinal angiomatous proliferation when choroidal neovascularization involves the fovea in patients with nAMD. During the drug induction period, aflibercept and ranibizumab are administered once a month, whereas brolucizumab is administered once every 6 weeks. During the maintenance period, either drug must be administered once every few months, depending on the drug and patient's condition.[8–10]

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Since the introduction of anti-VEGF drugs, the treatment results from clinical studies have shown significant improvements. Anti-VEGF drugs are the first-line treatment in Japan. Treatment guidelines in foreign countries, mainly regarding the intravitreal administration of anti-VEGF agents, are almost the same as those in Japan.[11,12]

However, retrospective studies have suggested that in clinical practice, patients are treated with fewer doses than in clinical trials, resulting in initial visual improvement but not long-term maintenance.[13,14] The relationship among the frequency of treatment, visual acuity improvement, and occurrence of adverse drug reactions has been described previously. It has been suggested that the possibility of visual improvement increases with an increase in the number of monthly injections; however, the incidence of endophthalmitis also increases.[15] The frequency of injections varies among physicians, and patient preferences vary based on fear of injection or infection, fear of recurrence, and desire for administration based on the burden of treatment.[15] Research have shown that patients with nAMD prefer less frequent treatment if there is a treatment that can maintain vision acuity. It is necessary to consider an optimal treatment policy from the perspective of burden and effect acquisition.[16,17]

A previous study showed that the management of nAMD can affect the quality of life of patients and their caregivers.[18] Caregivers face a high burden of treatment-related activities, including taking patients to hospital appointments, organizing medical appointments, and supporting them with their medications. In many patients and caregivers, difficulty in finding the right treatment option and cost, as well as the treatment itself (injection and the number and side effects of injections), have been shown to be obstacles associated with the management of nAMD.[19] In general, as treatments are tailored to the needs of patients and caregivers, treatments that are effective in clinical trials but are less acceptable to patients may result in poor patient adherence and may be less effective in routine clinical practice. Considering the patient and caregiver burdens of nAMD treatment, understanding patient preferences is important to determine the optimal treatment strategy for nAMD.[20,21]

Patient preference research to understand preferences is generally known to influence results by the way the question is asked (eg, items of a question to determine patients' preferences) and by the target population (eg, the individual's level of health literacy).[22–24] Therefore, to determine the preferences of patients with nAMD and other diseases systematically, it is important to evaluate multiple studies through a systematic review. Boyle et al conducted a systematic review of qualitative patient experiences with nAMD.[25] However, there has been no previous systematic review of patient preference surveys, partly because there are few preference surveys for nAMD.

As information concerning the preference of patients with nAMD can be evaluated by objective indices, such as relative importance, and because it was considered that patient preference can be effectively evaluated by investigating them, the purpose of this study was to systematically investigate the preference of patients with nAMD by conducting a systematic review focusing on quantitative preference surveys.

Materials and Methods

A systematic review was conducted according to the PRISMA 2020 Statement.[26]

Collection of Articles and Inclusion Criteria

We searched for articles on preferences for AMD treatment published between January 1, 2000, and December 31, 2023, using four databases: EMBASE, Google Scholar, MEDLINE, and PLOS. The terms used in the search were based on the method used by Sugitani.[27] Table 1 lists the search formulas used in this study.

For the article selection, a two-step screening was performed using the following inclusion criteria:

Articles had to be on a preference study: (i) for patients with AMD, caregivers, relatives, physicians, or healthy people with AMD; (ii) for treatment outcomes; (iii) for quantitative results; and (iv) for articles describing the original research. Duplicate articles were excluded from the analysis.

The titles and abstracts were reviewed for applicability in the primary screening, and the full texts were reviewed by two independent reviewers to assess eligibility for secondary screening. In the secondary screening, articles, in which only ranking was the output of the results and their importance was not quantified, were excluded.

Table 1 Search Strategy

Database	Search Formula
EMBASE	("conjoint analysis" /exp OR "conjoint analysis" OR "conjoint analyses" OR "choice behavior"/exp OR "choice behavior' OR "stated preference" OR "discrete choice" OR "latent class analysis"/exp OR "latent class analysis" OR "latent class analyses") AND ("age-related macular degeneration"/exp OR "age-related macular degeneration" OR "age-related macular edema") AND [2000–2023]/py
Google Scholar	("age-related macular degeneration" OR "age-related macular edema") AND ("conjoint analysis" OR "choice behavior" OR "choice behaviour" OR "stated preference" OR "discrete choice" OR "latent class analysis")
MEDLINE	("age-related macular degeneration" OR "age-related macular edema") AND ("conjoint analysis" OR "choice behavior" OR "stated preference" OR "discrete choice" OR "latent class analysis")
PLOS	(everything: "age-related macular degeneration" OR everything: "age-related macular edema") AND (everything: "conjoint analysis" OR everything: "choice behavior" OR everything: "stated preference" OR everything: "discrete choice" OR everything: "latent class analysis")

Article Review

The selected articles were reviewed and factors related to preference were examined, with the main results being the author, year of publication, target population, number of respondents, study design, year of survey, country of survey, patient demographics, relative importance, description of choice task, estimation method of relative importance and heterogeneity.

Results

Study Selection

In total, seven studies were extracted from 1156 studies (Figure 1).

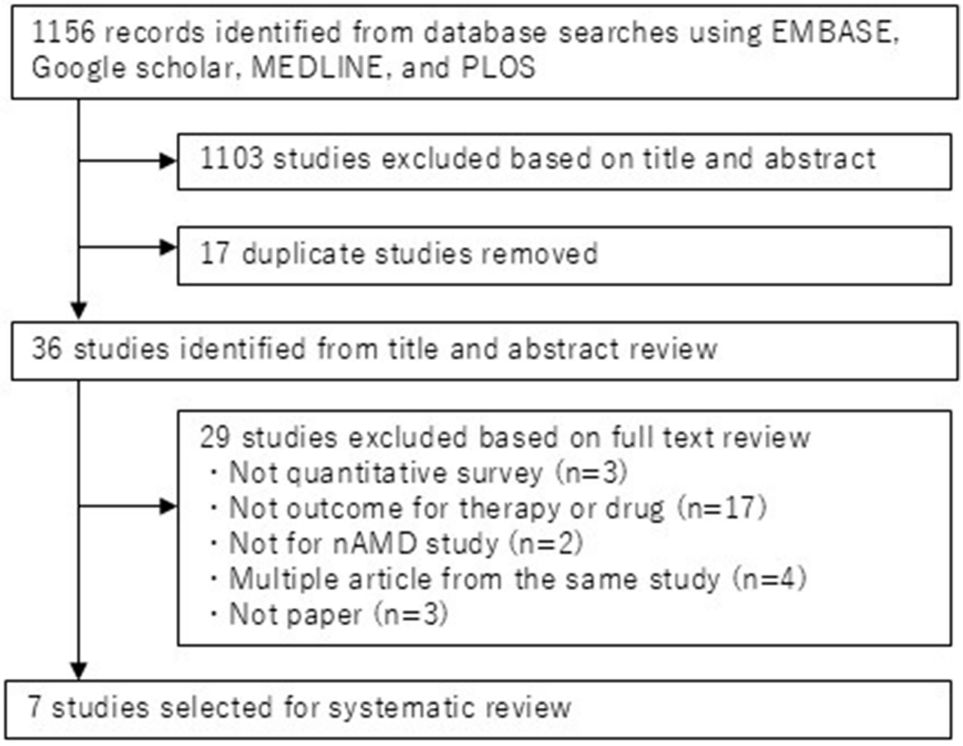

Figure 1 Flow diagram of the studies selection.

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Study Characteristics

The characteristics of these studies are presented in Table 2.[17,28–33] Conjoint analysis was used in all seven trials, of which six were Discrete Choice Experiments (DCEs) and one was a ranking. These studies were conducted in Germany (two studies), the US (one study), the UK (one study), Japan (one study), Spain (one study), and Singapore (one study). Target patients differed between studies. Six studies focused on patients with neovascular AMD (nAMD, also called wet AMD, ie, wAMD), and one focused on patients with nAMD or diabetic macular edema. Studies involving patients with dry AMD (dAMD) were not included.

Characteristics of Preference Studies

Information on the preference research methods used in the seven studies (number of alternatives, number of attributes, attributes and levels, blocks, number of tasks/patients, design and profile generation, and estimation method) is presented in Table 3.

The attributes of the treatments used in the seven studies were efficacy/safety (improvement in visual function, stabilization of visual function, effects on retinal fluid, side effects, and approval status), convenience (injection frequency, monitoring frequency, time required for each visit, and treatment regimen), and cost (cost to patients and cost to National Health Service [NHS]/insurance).

Table 3 includes the results of the assessment of quality and risk of bias. In terms of our assessment of quality, only one study adequately addressed all five elements of the PREFS checklist.[34] The average PREFS score was 3.86. All reports were adopted because the PREFS score was 3 or higher.

Results of Preference Studies

To visualize the differences in the relative importance of patients among the studies, the relative importance of each attribute in the seven studies is shown in Figure 2. Relative importance was calculated from the preference coefficient in a study by Vennedy et al[17] that did not have a relative importance. In Figure 2, deep gray indicates high relative importance, which is of great importance to patients. The attributes related to visual function, side effects, and approval status were summarized as attributes related to efficacy and safety. The frequency of injections, monitoring, and the time required for each visit were summarized as attributes related to convenience. The costs to patients and the NHS/insurance are summarized as attributes related to the cost. Although the definitions of attributes differed between studies, the following trends were observed.

Overall, the relative importance of attributes related to efficacy and safety was the highest, followed by those related to convenience and cost. The convenience and cost were almost equal. However, in two studies, attributes related to cost

Table 2 Study Characteristics

	Mueller et al[28]	**Vennedey et al[17]**	**Baxter et al[29]**	**Bhagat et al[30]**	**Joko et al[31]**	**Gallego-Pinazo et al[32]**	**Ozdemir et al[33]**
Publication year	2016	2016	2016	2020	2020	2021	2022
Any Funding by pharmaceutical company	Y	N	N	N	Y	Y	Y
Target population	nAMD	nAMD	nAMD	DME or nAMD	nAMD	nAMD	nAMD
Country	Germany	Germany	UK	USA	Japan	Spain	Singapore
No. of Pts. completed study	284	86	87	300	120	110	180
Method	DCE	DCE	CA (ranking)	DCE	DCE	DCE	DCE
Age (yr)	77.4 (Median)	–	81 (Median)	–	75.9 (Mean)	79 (Mean)	71.6 (Mean)
Female (%)	59.9	51	66	54	40.83	57.3	38.9
Visual acuity (%)	Poor: 22.9	Poor: 20 Very poor: 6	–	–	–	–	Good: 73.3 Moderate: 25.0 Poor: 1.7

Abbreviations: DCE, Discrete Choice Experiment; DME, Diabetic Macular Edema; nAMD, neovascular age-related macular degeneration; UK, United Kingdom; USA, United States of America.

Table 3 Characteristics of Preference Studies

Study	N Alternatives	N Attributes	Efficacy/ Safety	Convenience	Cost	N Tasks/ Patients	Design and Profile Generation	Estimation Method	Heterogeneity by Patient Demographic	PREFS Score
[28]	2 or more	3 (3 levels)	Change of VA in the next 12 months from the patient perspective	Treatment scheme		10	NA	Conditional Logit Regression Models	• Sex • Visual acuity level	5
[17]	2	5 (2–4 levels)	Effect on visual function	Monitoring frequency		12	Bayesian efficient design	Mixed multinomial logit model	–	3
			Side effects	Injection frequency						
			Approval status	The time a patient would need for each visit to the eye specialist, including travel, treatment, and waiting time						
[29]	10 (ranking)	7 (2–3 levels)	Vision	Frequency of visits—this is how often you have to come to clinic to be assessed (may require injection or not)	Cost to the NHS—treatment is always free at the point of delivery, but different treatments have different costs to the health service itself	10	NA	Stepwise linear regression models	• Age • Use of hospital transport	3
			Drug injection label—a drug can be used to treat different conditions	Length of wait—this is the average waiting time from arrival to finishing in the clinic per visit						
				Clinic setup—If an injection is required						
				Training of healthcare professional						

(*Continued*)

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Table 3 (Continued).

Study	N Alternatives	N Attributes	Efficacy/ Safety	Convenience	Cost	N Tasks/ Patients	Design and Profile Generation	Estimation Method	Heterogeneity by Patient Demographic	PREFS Score
[30]	2	5 (2–3 levels)	Vision	Frequency of treatments: How often you will have to come to the clinic to be assessed for possible treatment.	Cost per treatment to the insurance company	8	D-optimal design algorithm	Multinomial logistic regressionNelder–Mead simplex methodology	None	4
			Drug label status		Cost per treatment to you, the patient					
[31]	2	5 (3–4 levels)	Chance of visual acuity markedly improving after 12 months of treatment	Dosing regimen		24	A full profile, fractional, factorial, balanced, incomplete block design	Hierarchical Bayesian regression model, Conditional logit model	• Sex • Experience of anti-VEGF • Region (as determined by location of the hospital site)	4
			Chance of visual acuity maintenance after 2 years of treatment	Number of injections required in the first 12 months of treatment						
				Number of physician consultations in the first 12 months of treatment						
[32]	2	5 (2–3 levels)	Effect on visual function	Treatment regimen	Cost	NA	A factorial design (orthogonal main effect matrix)	mixed logit model	–	4
			Effects on retinal fluid	Monitoring frequency						
[33]	2	5 (2–4 levels)	Vision quality	Number of visits in a year	Yearly out-of-pocket cost	8	NA	Latent class logistic model	–	4
			Swelling in retina	Number of injections in a year						
			Drug label							

Abbreviations: P, purpose; R, respondents; E, explanation; F, findings; S, significance; VA, Visual Acuity; NA, Not applicable; AMD, Age-related macular degeneration; TV, television; FDA, Food and Drug Administration; NHS, National Health Service; PRN, Pro re nata; T&E, Treat and Extend; SGD, The Singapore dollar.

No	Survey year	Efficacy/Safety					Convenience			Cost	
		Improvement in visual function	Stabilization of visual function	Effects on retinal fluid	Side effects	Approval status	Injection frequency	Monitoring frequency	Time required for each visit**	Cost to patient	Cost to NHS/Insurance***
[28]	2012-2013	73.6					5.4		21.0		
[17]*	2014-2015	8.5			32.8	1.7	24.9	12.0			
[29]	2015	61				10		18			10
[30]	2018	40.4				21.3	12.2			23.1	3.0
[31]	2017-2018	16	34				31	19			
[32]	2018-2019	60.0		9.8			4.1	20.2		5.9	
[33]	2019-2021	34		11		12	4	15		24	

Figure 2 Standardized relative importance of attributes related to treatment.[17,28–33] Attributes of higher relative importance are black and attributes of lower relative importance are white. NHS National Health Service, * Calculated from range of each attribute in the paper, ** Waiting, treatment, and travel time, *** Cost to NHS,[29] Cost to Insurance.[30]

were included as costs to patients,[30,33] and the relative importance of cost was higher than that of convenience. The time required for each visit included waiting, treatment, and travel times. The cost of the NHS was included as an attribute in a study by Baxter et al.[29] The cost of insurance was included as an attribute in the study by Bhagat et al.[30]

Discussion

The relative importance of improvements in visual function varies among studies. This was extremely high in some studies and did not rank first in some studies. Overall, the relative importance of visual improvement in visual function tended to be low when side effects and patient costs were included as attributes. The attributes with a wide range of levels tended to be more important.

Comparing all studies,[17,28–33] the relative importance of improvement in visual function was the lowest (8.5%) in the study by Vennedy et al.[17] In this study, side effects were included as attributes, and their relative importance was 32.8%, which was the highest among all attributes. Additionally, a broader range of levels defined for injection and monitoring frequencies may increase the relative importance of these attributes and decrease the relative importance of improvements in visual function. This study did not define deterioration as the level of improvement in visual function, which may have influenced the importance of improvement in visual function. Regarding injection frequency, unlike other studies, this study defined "On demand, following monthly monitoring" as one of the levels of injection frequency, which may have resulted in a higher relative importance (24.9%) of injection frequency compared to other studies, as described above. These attributes, levels and relative importance are shown in Table 4.[17,28–33]

Table 4 The Attributes Related to Improvement in Visual Function

Improvement in Visual Function				
Study	**Attributes**	**Definition of Each Attribute**	**Level**	**Relative Importance, %**
[28]	Change of visual acuity	Change of VA in the next 12 months from the patient perspective	• VA remains stable with a high probability • VA improves markedly with a high probability • VA worsens markedly with a high probability	73.6
[17]	Effect on visual function	–	• Stabilization • Improvement	8.5

(*Continued*)

Table 4 (Continued).

Improvement in Visual Function				
Study	**Attributes**	**Definition of Each Attribute**	**Level**	**Relative Importance, %**
[29]	Vision	–	• Good—able to read small print/ prices in supermarkets with good lighting • Moderate—able to recognise faces and read newspaper headlines/writing on TV (not small print) • Poor—able to navigate around a room and make out large objects, not able to see faces/TV/read	61
[30]	Vision	–	• Good—Able to read small print in magazines/newspapers with good lighting. • Moderate—Able to recognize faces and read newspaper headlines/writing on TV (medium print). • Poor—Able to navigate around a room and make out large objects, but not able to see faces/TV/read clearly.	40.4
[31]	Chance of visual acuitymarkedly improving after 12 months of treatment	–	• 25 out of 100 people (25%) • 30 out of 100 people (30%) • 35 out of 100 people (35%) • 40 out of 100 people (40%)	16
[32]	Effect on visual function	Best-corrected visual acuity improvements from baseline	• Stable (no changes) • Improvement of more than 5 letters • Improvement from 1–5 letters	60.0
[33]	Vision quality	Studies show that injections help improve the vision of patients with AMD. These vision improvements tend to occur in the first 3 to 4 months after starting injections and stay the same in most cases as long as the patient does not miss a clinic visit.	• Good • Moderate • Poor	34

Abbreviations: VA, Visual Acuity; TV, Television; AMD, Age-related Macular Degeneration.

Next, we discuss the studies by Bhagat et al,[30] Gallego-Pinazo et al,[32] and Ozdemir et al,[33] which included the cost to the patient as an attribute. In the study by Bhagat et al,[30] costs for patients (low cost: $5, high cost: $70) and insurance (low cost: $50, high cost: $1200) were included, and their relative importance was 23.1 and 3.0%, respectively. In this study, deterioration was included as one level of improvement in visual function, and the relative importance of improvement in visual function was 40.4%. The relative importance of injection frequency was also relatively low (12.2%). Moreover, "Frequency of treatments" was included as an attribute in the interview form; however, the explanation to patients was "How often you will have to come to the clinic to be assessed for possible treatment.' This explanation is closer to the monitoring frequency than to the injection frequency. Only two levels (more frequent: every 4 weeks, less frequent: every 8 weeks) were defined for this attribute, which may have influenced its low relative importance.

In a study by Ozdemir et al,[33] the cost to patients was explicitly defined as "the annual copayment", with a broad range of levels (SGD 150/injection, SGD 400/injection, SGD 800/injection, and SGD 1500/injection). The relative importance of cost to patients was 24%, which was the highest among all studies. Improvement, stabilization, and deterioration were included as levels of improvement in visual function, and a broad range of injection and monitoring frequencies were defined. However, the relative importance of improvement in visual function was 34%, injection frequency was 4%, and monitoring frequency was 15%, which was not as high as in other studies. This may be attributed to the lower relative importance of these three attributes, owing to the greater importance of costs to patients.

Although Gallego–Pinazo et al[32] included cost as an attribute, its relative importance was 5.9%, which was lower than those reported by Bhagat et al[30] and Ozdemir et al,[33] which also include costs. This may be attributed to the fact that the range of levels in Gallego–Pinazo et al[32] was narrow (5% Decrease, Same cost, 10% Increase). Moreover, the entire cost of treatment or the cost to the patients was unclear in the interview form, which may have affected the results. Improvement in visual function had the third highest relative importance among all studies (60.0%). These attributes, definition of attributes, levels and relative importance of the studies which included the cost to the patient as an attribute are shown in Table 5.[29,30,32,33]

However, considering the studies by Mueller et al,[28] Baxter et al,[29] and Joko et al,[31] neither the cost to patients nor side effects were included as attributes. The study by Mueller et al[28] had only three attributes: improvement in visual function, injection frequency combined with monitoring frequency, and the time required for each visit. Deterioration was defined as one of the levels of visual function. Consequently, improvement in visual function was the most important attribute in a study by Mueller et al,[28] which was the highest among all studies.

Table 5 The Attributes Related to Cost to Patients, Cost to NHS/Insurance

Cost to patient				
Study	Attributes	Definition of each attribute	Levels	Relative importance
[30]	Cost per treatment to you, the patient	–	• Low cost: $5 • High cost: $70	23.1
[32]	Cost (treatment cost compared to current treatment)	–	• 10% Increase • Same cost • 5% Decrease	5.9
[33]	Yearly out-of-pocket cost	Out-of-pocket cost refers to the total amount you or your family have to pay in a year for all treatment related costs, including costs for eye tests, injections and consultations after deductions from your insurance and other subsidies.	• SGD 150/injection • SGD 400/injection • SGD 800/injection • SGD 1500/injection The costs shown to the respondents were annual total cost = cost per injection*number of injections in a year	24
Cost to NHS/Insurance				
Study	Attribute	Definition of each attribute	Level	Relative importance, %
[29]	Cost to the NHS	Treatment is always free at the point of delivery, but different treatments have different costs to the health service itself	• Low cost—£50 • High cost—£500	10
[30]	Cost per treatment to the insurance company	-	• Low cost: $50 • High cost: $1200	3.0

Abbreviations: NHS, National Health Service; SGD, The Singapore dollar.

Concerning the study by Baxter et al,[29] deterioration was defined as one of the levels of visual function. Monitoring frequency was included as an attribute, although injection frequency was not, and only two levels (4 weekly, 8 weekly) were defined as the levels of monitoring frequency. The cost of insurance was included as an attribute, although the cost to patients was not included. The relative importance of the improvement in visual function was high and was the second highest among all studies.

In the studies by Mueller et al[28] and Baxter et al,[29] neither the cost to patients nor the side effects were included as attributes, and also, deterioration was defined as one of the levels of visual function. This may have led to the finding that the improvement in visual function was the most important factor in each study. In the study by Joko et al,[31] only four attributes were included: improvement in visual function, stabilization of visual function, injection frequency, and monitoring frequency. Regarding the attributes of improved and stable visual function, the range of levels was narrow because, unlike other studies that assumed 100% improvement, a certain probability of improvement was assumed, and deterioration of visual function was not defined as one of the levels. Therefore, the relative importance of improvement on visual function and stabilization of visual function did not increase and was comparable to that of the injection and monitoring frequencies (especially the injection frequency).

Considering how the question on efficacy preferences differed between studies, all studies except for that conducted by Joko et al[31] included improvement in visual function and/or stabilization of visual function as attributes and defined two or three levels. As aforementioned, only stabilization and improvement were defined as levels of efficacy, and deterioration was not defined as one of the levels of efficacy in the studies by Vennedy et al[17] and Gallego–Pinazo et al;[32] however, deterioration, stabilization, and improvement were defined as levels of efficacy in the studies by Mueller et al,[28] Baxter et al,[29] and Ozdemir et al.[33] Conversely, Joko et al[31] was characterized by including "significant improvement of visual function" and "stabilization of visual function" as separate attributes and defined the respective levels as the probability, such as "Chance of visual acuity markedly improving after 12 months of treatment (25%, 30%, 35%, or 40%)" and "Chance of visual acuity maintenance after 2 years of treatment (80%, 93%, or 96%) (See Table 4). "In the studies by Gallego–Pinazo et al[32] and Ozdemir et al,[33] the effect on retinal edema was included separately from the effect on visual function. In the study by Gallego–Pinazo et al,[32] "reduction", "resolution", and "no change" were defined as levels of "effects on retinal fluid" (see Table 4). In contrast, in the study by Ozdemir et al,[33] "well-controlled swelling", "moderately-controlled swelling", and "poor-controlled swelling" were defined as levels of "swelling in retina" (See Table 3). As described above, the difference between the levels increased when deterioration was defined as one of the levels of improvement in visual function. As a result, the relative importance of the attribute of improvement in visual function tended to be higher. Therefore, the effect on retinal edema in the study by Ozdemir et al,[33] which included deterioration, had a slightly higher relative importance than that in the study by Gallego–Pinazo et al,[32] which did not include deterioration.

The discussion has focused on the perspective of efficacy thus far. Next, we discuss the aspects of costs and injection frequency and monitoring frequency.

In the study by Vennedy et al,[17] not only the regular scheduled injection, such as "every month", "every 2 months", and "every 4 months" but also "on demand, following monthly monitoring" were defined as levels of injection frequency, and the latter tended to be preferred. In contrast, in the study by Mueller et al,[28] "pro re nata (PRN) scheme meaning eye examination every 4 weeks combined injection if needed" was also defined, but scheduled injection every 4 weeks was preferred. This was particularly true in women and patients with intermediate visual function. In the study by Gallego–Pinazo et al,[32] "every 3 months", "every 2 months" and "every month" were defined as levels of attribute "monitoring frequency (follow up visits)" and "fixed" and "variable (PRN or treat-and-extend(T&E))" were defined as levels of attribute "Treatment regimen". Less frequent monitoring was preferred, and the relative importance of "Monitoring frequency" was high next to its "Effect on visual function". Conversely, for "Treatment regimen", "Fixed" was 0.000 and "Variable (PRN or T&E)" was 0.335 in terms of utility, suggesting that "Variable (PRN or T&E)" seemed to be preferred.

Cost was included as an attribute in the studies by Baxter et al,[29] Bhagat et al,[30] Gallego–Pinazo et al,[32] and Ozdemir et al[33] "Costs to NHS" was included as an attribute in the study by Baxter et al[29] and "Cost per treatment to the insurance company" was included in the study by Bhagat et al.[30] This may be attributed to the fact that the studies were conducted academically. Only studies that did not receive funding support from pharmaceutical companies included cost as a

attribute, suggesting that the presence or absence of pharmaceutical company involvement affected whether cost was included as a attribute. In a study by Baxter et al,[29] the NHS is a tax-funded service in the UK, and NHS members can receive medical care from physicians without co-payment. The participants were patients who visited clinics dedicated to AMD management in a publicly funded (NHS) University Hospital. As medical expenses are free for these patients, it seems that the cost to the patients was not considered an attribute, and only the "Cost to the NHS" was included. In a study by Bhagat et al,[30] these attributes were determined based on the results of a survey of three small focus groups, with five patients each who had received three or more anti-VEGF injections in the previous stage of research. The definition of cost differed significantly among the studies by Baxter et al,[29] Bhagat et al,[30] Gallego–Pinazo et al,[32] and Ozdemir et al.[33] In the study by Baxter et al,[29] "Low cost - £50" and "High cost - £500" were defined as levels of "Cost to the NHS- treatment is always free at the point of delivery, but different treatments have different costs to the health service itself". In the study by Bhagat et al,[30] "Low cost: $50" and "High cost: $1200" were defined as levels of "Cost per treatment to the insurance company", and "Low cost: $5" and "High cost: $70" were defined as levels of "Cost per treatment to you, the patient". In the study by Gallego–Pinazo et al,[32] "Decrease 5%", "Same cost", and "Increase 10%" were defined as levels of cost. The questionnaire did not clearly indicate whether it was the entire cost of treatment or the actual cost paid by the patients. Regarding the study by Ozdemir et al,[33] attribute "Yearly out-of-pocket cost" described that "The costs shown to the responders were annual total cost = cost per injection * number of injections in a year". "SGD 150/injection", "SGD 400/injection", "SGD 800/injection", and "SGD 1500/injection" were defined as levels of this attribute. The study by Joko et al[31] was the only one conducted after 2016 and cost was not included as an attribute. This study was conducted in Japan, where the national health insurance system applies to all citizens, and the upper limit of the self-pay burden is fixed because an amount exceeding a certain amount is refunded later. Therefore, the patient preference survey may not have paid attention to costs and did not include them in its attributes.

Regarding the drugs used previously, the proportion of patients who used Eylea was 4.2% in the study by Mueller et al,[28] while it was 41% in the study by Vennedy et al.[17] A patient preference survey was conducted from 2012 to 2013 by Mueller et al[28] and from 2014 to 2015 in the study by Vennedy et al.[17] As Eylea has been used since 2012, it became more popular during the survey by Vennedy et al[17] was conducted. Eylea is listed on the US label as being effective every 2 months in the 1st year, after which the dosing interval can be extended to 12 weeks (T&E). The Eylea T&E regimen is also recommended in Asia.[35] A post-marketing study, CENTERA, conducted in Europe between 2016 and 2019 also showed that the T&E regimen of EYLEA was effective.[36] Survey by Vennedy et al.[17] Eylea (T&E) has become popular, and flexible injection regimens may be more acceptable than those reported by Mueller et al.[28] In some studies, including those by Mueller et al,[28] Vennedy et al,[17] Baxter et al,[29] Gallego–Pinazo et al,[32] and Ozdemir et al,[33] injection experience was included as an eligibility criterion. Injection experience is known to influence preference;[27,37] however, no clear trends were observed, partly because the number of studies was insufficient. Further, in the studies by Mueller et al[28] and Vennedy et al,[17] at least one intravitreous injection was defined as the eligibility criterion. Ozdemir et al[33] defined the underlying anti-VEGF treatment. The relative importance of improvement in visual function was 73.6, 8.5, and 34% in the studies by Mueller et al,[28] Vennedy et al,[17] and Ozdemir et al,[33] respectively. Concerning the studies by Baxter et al[29] and Gallego–Pinazo et al,[32] more abundant injection experience was included as an eligibility criterion. "At least 3 previous injections" was included in the study by Baxter et al,[29] while "anti-VEGF drugs for at least 2 years" was included in the study by Gallego–Pinazo et al.[32] Baxter et al[29] and Gallego–Pinazo et al,[32] the relative importance of improvement in visual function was the highest compared to other attributes in each study (61 and 60% in the studies by Baxter et al[29] and Gallego-Pinazo et al,[32] respectively). However, injection experience was not included as an eligibility criterion in the studies by Bhagat et al[30] and Joko et al.[31] Bhagat et al[30] investigated patients who received three or more anti-VEGF injections to determine their attributes before DCE; however, no particular criteria were specified for the entire population. Patients were enrolled in the study by Joko et al, regardless of the presence or absence of prior anti-VEGF therapy.[31] The relative importance of visual function improvement was 40.4% in a study by Bhagat et al[30] and 16% in a study by Joko et al.[31]

Mueller et al,[28] Bhagat et al,[30] Joko et al,[31] and Gallego–Pinazo et al[32] described the relationship between patient demographics and preference. Several studies stated that sex differences lead to differences in preferences. Regarding sex, in a study by Mueller et al,[28] the utility value of treatment every 4 weeks tended to be higher and more preferred than

that of PRN in women and patients with moderate visual function. The authors suggested that these patients were willing to accept the high burden of maintaining, or even improving, their visual function. In a study by Joko et al,[31] women tended to prefer the best T&E profile, whereas men tended to prefer the best PRN profile. The authors hypothesized that this sex difference was attributed to different perceptions of investment in expected benefits from previous studies; however, they stated that this hypothesis requires further investigation. In the studies by Mueller et al[28] and Joko et al,[31] female patients tended to prefer the fixed regimen and TAE to PRN compared to male patients. PRN is an administered regimen that patients receive when their symptoms worsen. TAE is a regimen administered before symptoms worsen, and the injection interval gradually increased. This may be attributed to the tendency of female patients to not prefer PRN because of the fear of worsening symptoms. In both articles, 59.9% were women in Mueller et al[28] and 40.83% were women in Joko et al.[31] Approximately half of the subjects were female, showing no significant difference, suggesting that the gender ratio does not significantly affect the discussion.

Other than sex, age was a comparable baseline factor. The mean age is 77.4 years in Mueller et al[28] and 75.90 years in Joko et al.[31] The mean age was slightly lower at Joko et al,[31] but there is no major difference.

There was a consistent tendency for no difference in preference by age in the studies by Mueller et al[28] and Bhagat et al.[30] There were no consistent trends in other variables among the studies. In addition, the relationship between patient demographics and preferences was not described by Vennedy et al,[17] Baxter et al,[29] and Ozdemir et al.[33]

This study has some limitations.

One limitation is that patient preference studies from third world were not included in this systematic review. Although this study did not focus specifically on developed countries, patient preference studies in third world were not available. Consequently, only studies from Germany, United States, United Kingdom, Japan, Spain, and Singapore were included. Given that the economic burden affects the uptake of anti-VEGF agents in several third world including India,[38–40] there may be limitations in considering our findings as global patient preferences, including third world.

A second limitation is that it is necessary to be careful in using the relative importance among different studies. As described, it is assumed that selection of attributes and levels and the differences in the target patient population affect the relative importance.

Conclusion

Although the definitions of treatment attributes differed among the studies, patients with nAMD considered efficacy and safety to be the most important. The results of several studies suggest that patient preferences may be affected by patient demographics, such as sex. Although there are currently only a few preference studies on patients with AMD, it is necessary to continue conducting studies to understand the trends in patient preferences according to patient demographics.

Data Sharing Statement

All data generated in this systematic review are included in this published article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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