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ORIGINAL ARTICLE

Priority options of anti-vascular endothelial growth factor agents in wet age-related macular degeneration under the National Health Insurance Program

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Abstract

Background: Age-related macular degeneration (AMD) is a leading cause of blindness worldwide, for which intravitreal injection of anti-vascular endothelial growth factor (VEGF) is the primary treatment option. The purpose of the current study was to investigate the prioritization of anti-VEGF agents for wet AMD under the National Health Insurance (NHI) Program, and their clinical outcomes.

Methods: Patients who were diagnosed with active choroidal neovascularization caused by AMD, and who met the criteria for reimbursement for anti-VEGF therapy by the NHI program in Taiwan between August 1, 2014 and May 31, 2015, were included in the study. Factors potentially influencing the choice of treatment agent were analyzed, and clinical outcomes were compared between the two different agents and their protocols.

Results: A total of 166 treatment applications in 166 eyes from 159 patients were enrolled in the study. Age, laterality, presence of retinal pigment epithelial detachment, history of hypertension, coronary artery disease, and cerebral vascular accidents were significantly associated with the selection of the anti-VEGF agent. Treatment patterns and clinical outcomes were similar between the patients treated with ranibizumab and those treated with aflibercept. Significantly fewer injections were given during the follow-up period in those treated with aflibercept.

Conclusion: Under the restrictive insurance program in Taiwan, more patients and ophthalmologists chose to treat wet AMD using aflibercept. However, in clinical practice, no significant differences in efficacy or clinical outcomes were found between the patients treated with ranibizumab and those treated with aflibercept.

Keywords: Aflibercept; Age-related macular degeneration; National Health Insurance; Ranibizumab

1. INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of blindness worldwide,[1,2] for which intravitreal injections of anti-vascular endothelial growth factor (VEGF) are the primary treatment of choice.[2] Of these anti-VEGF agents, ranibizumab and aflibercept are the most commonly used. Previous studies have reported on the strong effects of reducing retinal pigment epithelial detachment (RPED) with aflibercept therapy.[3–6] Other studies have reported that because aflibercept is a recombinant fusion protein, which is composed of an Fc domain, it can facilitate systemic absorption.[7–9] However, in the VIEW 1 and VIEW 2 trials and 2 "real-world" studies, no significant differences in clinical efficacy or systemic side effects were noted between the two drugs.[10–13] Therefore, the prioritization of anti-VEGF agents for AMD treatment remains controversial.

In Taiwan, ranibizumab was approved for AMD treatment by the National Health Insurance (NHI) program in January 2011, and aflibercept was approved in August 2014. Each eye of a patient can be reimbursed for 3 to 7 doses of either anti-VEGF agent, in a 2-year period after the administration is proposed by an approved ophthalmologist. However, switching between the two agents is restricted, meaning that ophthalmologists and patients have to choose between the agents at the initial application regardless of the following treatment outcome.

The current study aimed to understand the real-world treatment options, as well as the patterns and outcomes in patients with AMD under the NHI program. The primary endpoint was to analyze the patient characteristics and clinical factors, which affect the selection of one of the anti-VEGF agents. The secondary endpoint was to evaluate the clinical outcomes following this decision.

2. METHODS

2.1. Criteria for reimbursement of anti-VEGF agents in Taiwan

Under the NHI program in Taiwan, the following criteria must be met for the reimbursement of anti-VEGF agents:

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1. Patient should be aged ≥50 years and has been diagnosed with AMD based on fundus photography, fluorescence angiography, and optical coherence tomography.
2. Best-corrected visual acuity (BCVA) should be between 20/40 and 20/400, as tested by Snellen equivalent.
3. Patients with polypoidal choroidal vasculopathy confirmed by indocyanine green angiography should be excluded.
4. Patients with choroidal neovascularization due to etiologies other than AMD (such as high myopia or uveitis) or advanced macular scarring, subretinal fibrosis, and geographic atrophy should be excluded.
5. Up to three doses of anti-VEGF agent are allowed for the initial application, with an additional four doses permitted only if the first reimbursed treatment was effective. All approved treatments should be completed within 2 years.
6. Changing or switching between the two anti-VEGF agents is restricted during treatment.

2.2. Study design and targets

The present retrospective study was conducted as a hospital-based chart review. All patients who were diagnosed with AMD between August 1, 2014 and May 31, 2015 at Taipei Veterans General Hospital and met the criteria for reimbursement of anti-VEGF therapy were enrolled in the study. The patients who lacked complete medical records, ophthalmic examination results or were not followed for at least 6 months were excluded. The study was approved by the institutional review board of the Taipei Veterans General Hospital.

2.3. Factors influencing the choice of anti-VEGF agent

To investigate the factors that may influence the selection of an anti-VEGF agent, the characteristics of ophthalmologists and patients were analyzed. A total of eight experienced retinal specialists worked at Taipei Veterans General Hospital during the study period, three of whom were female and five of whom were male. Seniority was assigned if the ophthalmologist had worked as a retinal specialist for >10 years. The patient's age, BCVA, central macular thickness (CMT), history of AMD in the other eye, presence of RPED, and medical history of cardiovascular disease before drug application were analyzed.

2.4. Clinical outcomes

Treatment patterns and clinical outcomes were compared between the patients who were treated with ranibizumab and aflibercept. The presence of RPED at the last visit, the total treatment dose, final CMT, difference in CMT compared with prior to treatment, and BCVA at 4 and 6 months after the initial intravitreal injection were analyzed.

2.5. Statistical analysis

Statistical analysis was performed using SPSS software version 18.0 (SPSS, Inc., Chicago, Illinois, USA). The χ^2 test and two-sample student *t*-test were used for data analysis between groups. A *p*-value of <0.05 was considered to indicate a statistically significant difference.

3. RESULTS

A total of 166 treatment applications from 159 patients were reviewed. Among them, 43 applications were for ranibizumab and 123 were for aflibercept. Only 69.9% of the applications (65.1% for ranibizumab and 71.5% for aflibercept) were approved for reimbursement. The most common reasons for disapproval were "a large proportion of fibrovascular scarring" and "polypoidal choroidal vasculopathy was suspected".

There were significantly more applications of aflibercept compared with ranibizumab ($p = 0.01$). Univariate analysis showed that in general, patients who applied for aflibercept were younger, had a history of AMD in the other eye, had RPED, and had no history of hypertension, coronary artery disease, or cerebral vascular accidents, compared with those who applied for ranibizumab (Table 1). There were no significant differences between those who applied for ranibizumab or aflibercept with regards to their BCVA, CMT, or the seniority or sex of their ophthalmologist.

Due to the limits on the total dose allowed by the NHI program, only 46.4% and 34.1% of patients received 3 monthly injections of ranibizumab and aflibercept, respectively, for the initial loading dose. It should be noted that an increased proportion of patients were treated without three loading injections when they were treated by a junior or female ophthalmologist. However, no significant differences in clinical or anatomical outcomes were noted between the patients who did and did not receive loading injections (Tables 2 and 3).

The total number of injections within 6 months was significantly lower in the patients treated with aflibercept compared with those treated with ranibizumab (2.8 vs 3.0; $p < 0.01$). There were no significant differences observed in improvement of RPED, final CMT, difference in CMT, BCVA and improvement in BCVA 4 and 6 months after the initial therapy, between patients treated with ranibizumab or aflibercept (Table 4).

4. DISCUSSION

Treatment of wet AMD with anti-VEGF medications can improve or stabilize vision in a large proportion of patients who would otherwise progress to blindness within 1 to 2 years.[2,14,15] Differences in disease management strategies are likely to be associated with the healthcare system, and include reimbursement, selection of patients for treatment, and the number of permitted injections.[16] However, little is known about the prioritization and selection of anti-VEGF agents and their treatment patterns and clinical outcomes in a real-world setting, under restrictions set by health insurance programs. Moreover, due to the offer of full reimbursement, the cost of anti-VEGF agents is not a confounding factor. The current study was conducted to better understand the real-world treatment strategy of wet AMD under the NHI Program in Taiwan.

Following the analysis of factors influencing decision making, it was found that initial BCVA and CMT were not major considerations when choosing the therapy. Although there were consistently more applications for aflibercept, there were a notably increased number of applications for ranibizumab in patients who were older or had a history of hypertension, coronary artery disease, or cerebral vascular accidents. This suggests that systemic safety is an important consideration, as anti-VEGF injections can increase the risk of systemic thrombotic cardiovascular events. The terminal elimination half-life of free aflibercept in plasma has been reported to be approximately 5 to 6 days after intravitreal administration (Eylea [package insert], Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2011). In comparison, ranibizumab has been reported to have a short systemic half-life of 0.09 days after intravitreal injection.[9] However, no significant differences in systemic or ocular safety were noted in the VIEW 1 and VIEW 2 randomized trials, which compared the efficacy of aflibercept and ranibizumab for the treatment of AMD.[11] Therefore, there is still no consensus on differences in systemic exposure or side effects following the intravitreal injection of these two drugs.

In the current study, patients who had a history of AMD in the other eye were more likely to choose aflibercept than ranibizumab to treat AMD. Since aflibercept was not approved for

Table 1

Decision making for anti-VEGF medications

Variables	Ranibizumab n = 43		Aflibercept n = 123		*p*
Seniority of clinicians					
Senior (n, %)	19	(26.4%)	53	(73.6%)	0.08
Junior (n, %)	24	(40.7%)	35	(59.3%)	
Sex of clinicians					
Male (n, %)	27	(30.3%)	62	(69.7%)	0.38
Female (n, %)	16	(38.1%)	26	(61.9%)	
Age					
Years (mean, SD)	83.2	±8.3	78.1	±8.9	<0.01
HTN/CAD/CVA					
Yes (n, %)	26	(36.1%)	46	(63.9%)	0.01
No (n, %)	17	(18.1%)	77	(81.9%)	
AMD in the fellow eye					
Yes (n, %)	14	(18.7%)	61	(81.3%)	0.05
No (n, %)	29	(31.9%)	62	(68.1%)	
RPED					
Yes (n, %)	14	(14.3%)	84	(85.7%)	<0.01
No (n, %)	29	(42.6%)	39	(57.4%)	
Visual acuity					
LogMAR (mean, SD)	0.82	±0.45	0.71	±0.37	0.10
Central macular thickness					
(μm) (mean, SD)	332.6	±88.5	336.8	±132.5	0.82

Univariate analysis was performed using the χ^2 test and two-sample *t* test.

AMD = age-related macular degeneration; Anti-VEGF = anti-vascular endothelium growth factor; HTN/CAD/CVA = hypertension/coronary artery disease/cerebral vascular accident; RPED = retinal pigment epithelial detachment.

Table 2

Decision making for different treatment schedule

Variables	Loading dose n = 43		PRN[a] n = 73		*p*
Medications					
Ranibizumab (n, %)	13	(46.4%)	15	(53.6%)	0.24
Aflibercept (n, %)	30	(34.1%)	58	(65.9%)	
Seniority of clinicians					
Senior (n, %)	36	(56.3%)	28	(43.8%)	<0.01
Junior (n, %)	7	(13.5%)	45	(86.5%)	
Sex of clinicians					
Male (n, %)	37	(46.3%)	43	(53.7%)	<0.01
Female (n, %)	6	(16.7%)	30	(83.3%)	
Age					
Years (mean, SD)	79.7	±9.4	79.3	±8.3	0.79
HTN/CAD/CVA					
Yes (n, %)	15	(28.3%)	38	(71.7%)	0.07
No (n, %)	28	(44.4%)	35	(55.6%)	
AMD in fellow eye					
Yes (n, %)	20	(42.6%)	27	(57.4%)	0.31
No (n, %)	23	(33.3%)	46	(66.7%)	
RPED					
Yes (n, %)	31	(43.1%)	41	(56.9%)	0.09
No (n, %)	12	(27.3%)	32	(72.7%)	
Visual acuity					
LogMAR (mean, SD)	0.72	±0.42	0.75	±0.35	0.75
Central macular thickness					
(μm) (mean, SD)	342.5	±105.2	331.7	±134.8	0.63

Univariate analysis was performed using the χ^2 test and two-sample *t* test.

[a]PRN: pro re nata, treated as needed.

AMD = age-related macular degeneration; HTN/CAD/CVA = hypertension/coronary artery disease/cerebral vascular accident; RPED = retinal pigment epithelial detachment.

Table 3

Clinical outcomes of different treatment schedules

Variables	Loading dose n = 43		PRN[a] n = 73		*p*
Medications					
Ranibizumab (n, %)	13	(46.4%)	15	(53.6%)	0.24
Aflibercept (n,%)	30	(34.1%)	58	(65.9%)	
RPED at last visit					
Yes (n, %)	16	(42.1%)	10	(33.3%)	0.46
RPED improvement					
Yes (n, %)	12	(44.4%)	7	(43.8%)	0.97
Final CMT					
(μm) (mean, SD)	218.6	±35.0	221.7	± 48.9	0.50
CMT reduction					
(μm) (mean, SD)	110.1	±93.4	103.5	± 91.9	0.49
VA at month 4					
LogMAR (mean, SD)	0.65	±0.43	0.77	± 0.68	0.58
VA at month 6					
LogMAR (mean, SD)	0.65	±0.44	0.72	± 0.60	0.47
VA improvement month 4					
LogMAR (mean, SD)	–0.06	±0.28	0.12	± 0.52	0.15
VA improvement month 6					
LogMAR (mean, SD)	–0.05	±0.31	0.09	± 0.53	0.28

Univariate analysis was performed using the χ^2 test and two-sample *t* test.

[a]PRN: pro re nata, treated as needed.

CMT = central macular thickness; RPED = retinal pigment epithelial detachment; VA = visual acuity.

Table 4

Clinical outcomes of different anti-VEGF medications

Variables	Ranibizumab		Aflibercept		*p*
Approval by NHI					
Yes (n, %)	28	(65.1%)	88	(71.5%)	0.43
Three loading doses					
Yes (n, %)	13	(46.4%)	30	(34.1%)	0.24
PED at last visit					
Yes (n, %)	5	(22.7%)	21	(45.7%)	0.07
PED improvement					
Yes (n, %)	4	(57.1%)	15	(41.7%)	0.45
Total injections					
n (mean, SD)	3.0	±0.4	2.8	±0.5	<0.01
Final CMT					
(μm) (mean, SD)	221.7	±28.7	220.4	±45.4	0.28
CMT reduction					
(μm) (mean, SD)	99.3	±63.8	109.3	±103.7	0.89
VA at month 4					
LogMAR (mean, SD)	0.58	±0.39	0.74	±0.60	0.68
VA at month 6					
LogMAR (mean, SD)	0.59	±0.40	0.72	±0.60	0.64
VA improvement month 4					
LogMAR (mean, SD)	–0.06	±0.22	0.03	±0.45	0.18
VA improvement month 6					
LogMAR (mean, SD)	–0.05	±0.23	0.01	±0.48	0.78

Univariate analysis was performed using the χ^2 test and two-sample *t* test.

Anti-VEGF = anti-vascular endothelium growth factor; CMT = central macular thickness; NHI = National Health Insurance; PED = retinal pigment epithelial detachment; VA = visual acuity.

reimbursement in Taiwan until August 2014, it is possible that the other eyes of most of these patients were treated with either ranibizumab or bevacizumab, or a different treatment option. Even though no significant difference in efficacy has been reported between aflibercept and ranibizumab, previous studies have shown some improvements in anatomical and even functional outcomes, when aflibercept was used to treat patients who did not respond well to ranibizumab.[4–6,17–23] The authors hypothesize that one of the reasons for this finding may be because some patients and ophthalmologists choose to treat the newly affected eye with aflibercept if the response was not satisfying following treatment with ranibizumab in the other eye.

The pathophysiology of the association between RPED and AMD is unclear. A previous study reported that RPED is an important predictive factor of vision loss in patients with AMD.[24] In addition, Pepple et al reported that about half of all

patients with AMD and newly diagnosed RPED experienced an average vision loss of >3 lines over a 1-year follow-up period.[25] Previous large randomized trials reported that patients treated with aflibercept had higher rates of RPED flattening compared with those receiving ranibizumab over 52 weeks of follow-up.[3,10,11] Furthermore, other studies have shown a good response in the height, size, and total regression of RPED in patients treated with aflibercept.[3–6] This may be the main reason why there were a higher proportion of applications for aflibercept compared with ranibizumab in patients presenting with RPED in their affected eyes. However, selection bias could also explain the finding of no difference in RPED improvement between the two groups.

Only 34% to 46% of the patients received three loading doses of anti-VEGF injections, even though receiving an initial loading dose has been reported to result in greater improvements in visual acuity.[16] However, due to treatment burden and the limited number of approved doses, the results show that ophthalmologists in Taiwan favor a pro re nata strategy to minimize the number of injections made under the reimbursement policy. No significant differences were found in the clinical outcomes between patients with or without the three loading doses. Furthermore, a previous study reported that the use of a loading dose was important to maximize the initial gain in vision, but that it did not seem to influence the rate of decline in visual acuity during 2 years of follow-up.[16] This may further explain why >50% of the eyes with AMD had their approved medication injected under the pro re nata strategy.

With regard to clinical outcomes, significantly fewer injections were found in patients receiving aflibercept compared with those receiving ranibizumab within a 6-month period. Although the VIEW 1 and VIEW 2 trials demonstrated a longer duration of efficacy using aflibercept, several other clinical observational studies reported no difference in the number of injections between the two drugs.[12,13] No other differences in clinical outcomes were identified between the two drugs, including improvements in BCVA or CMT at 4 or 6 months after treatment.

There were some limitations to the present study. First, as the study was retrospective, selection bias could exist. For example, although the initial visual acuity and CMT were not different between the two groups, the height and amount of subretinal fluid might influence the decision of the patients and clinicians, and these factors may also affect the final outcome. Second, the treatment strategy used in the current study was restricted due to the role of the NHI in Taiwan. Therefore, it was not possible to analyze the effectiveness of shifting from one agent to the other, or combination therapy with other medications, such as steroid or photodynamic therapy. Finally, the insurance program only reimbursed up to seven injections, under treatment definitely occurred in patients who required more frequent injections, which could have led to the relatively poor outcomes observed in the patients.

In conclusion, the results indicate that age, laterality, presence of RPED, and history of cardiovascular disease were key concerns for patients and ophthalmologists when choosing their anti-VEGF drug. Under the restrictive insurance program in Taiwan, more patients and ophthalmologists tend to choose aflibercept for the treatment of wet AMD, due to the presumed superior efficacy of this agent. However, in clinical practice, no significant difference in efficacy of clinical outcomes was found between patients treated with ranibizumab and aflibercept. However, fewer injections were administered to patients treated with aflibercept. Large, prospective studies may be needed to investigate the long-term treatment efficacy and safety of these two drugs to reduce the trade-off between treatment burden and clinical outcomes.

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