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RETINAL DISORDERS

Difference in treatment burden of neovascular age-related macular degeneration among different types of neovascularization

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Abstract

Purpose To evaluate the difference in the treatment burden among different types of neovascular age-related macular degeneration (AMD).

Methods This retrospective, observational study included 431 patients who were diagnosed with neovascular AMD. Patients were divided into three groups: type 1 or 2 neovascularization group ($n = 167$), type 3 neovascularization group ($n = 50$), and polypoidal choroidal vasculopathy (PCV) group ($n = 214$). The number of hospital visits per year and the number of anti-vascular endothelial growth factor (VEGF) injections per year were compared among these groups. Furthermore, the incidence of bilateral involvement during the follow-up period was compared among the groups.

Results The mean follow-up period was 50.6 ± 11.3 months. The number of hospital visits per year was significantly higher in the type 1 or 2 neovascularization group (mean: 6.1 ± 1.5) and type 3 neovascularization (6.6 ± 1.6) than in the PCV group (6.0 ± 1.5) ($P < 0.001$). The number of anti-VEGF injections per year was significantly higher in type 3 neovascularization group (3.1 ± 1.7) than in the type 1 or 2 neovascularization group (2.3 ± 1.5) or the PCV group (2.3 ± 1.2) ($P = 0.042$). There was a significant difference in the incidence of bilateral involvement among patients in type 1 or 2 neovascularization group (20.4%), type 3 neovascularization group (46.0%), and the PCV group (15.4%) ($P < 0.001$).

Conclusions The high frequency of hospital visits and that of anti-VEGF injections in patients with type 3 neovascularization suggests high treatment burden in these patients. The high incidence of bilateral involvement could be one of the primary reasons for high treatment burden in patients with type 3 neovascularization.

Keywords Age-related macular degeneration · Choroidal neovascularization · Retinal angiomatous proliferation · Type 3 neovascularization · Polypoidal choroidal vasculopathy · Burden

Key messages

- *What is known?
  : Treatment of neovascular age-related macular degeneration places an enormous economic and time burden on patients. To date, differences in the treatment burden among different types of neovascularization have not yet been elucidated.
- *What is new information?
  : The frequency of hospital visits and that of anti-vascular endothelial growth factor injections in patients with type 3 neovascularization is higher than in those with other types of neovascularization. High incidence of bilateral involvement in patients with type 3 neovascularization could have contributed to this difference.

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Introduction

Neovascular age-related macular degeneration (AMD) is a vision-threatening disease that can lead to severe visual impairment [1, 2]. The advent of anti-vascular endothelial growth factor (VEGF) therapy has significantly improved visual prognosis of neovascular AMD [3]. However, anti-VEGF therapy places an enormous economic and time burden on patients. Moreover, with increasing number of patients suffering from AMD worldwide, the treatment burden on them has been regarded as an important global issue [4–6].

Until now, numerous studies have evaluated treatment burden of neovascular AMD on patients. However, differences in the treatment burden among different types of neovascularization have not yet been elucidated. Type 3 neovascularization [7], also known as retinal angiomatous proliferation [8], is a subtype of neovascular AMD that is characterized by intraretinal neovascularization. It constitutes 4.5 to 15% of all neovascular AMD cases [9–11]. Although type 3 neovascularization had previously been considered as refractory to treatment, the advent of anti-VEGF has markedly improved treatment outcomes [12, 13]. Polypoidal choroidal vasculopathy (PCV) is another peculiar kind of neovascularization [14], which is prevalent in the Asian population [10]. There has been a controversy on whether PCV is a subtype of neovascular AMD [15, 16]. However, similar to neovascular AMD, anti-VEGF therapy is the mainstay of PCV treatment [17]. Thus, the treatment burden caused by long-term anti-VEGF therapy is an important issue in PCV as well.

Neovascular AMD often shows bilateral involvement [18]. One of the interesting findings is that the incidence of bilateral involvement is different among different subtypes of neovascularization [19–21]. It is possible that this difference may influence the treatment burden on patients.

Knowledge regarding the difference in treatment burden among different types of neovascularization may assist physicians to establish proper management plans for patients. In addition, it may aid the policy makers to develop individualized health/insurance policies for patients with a certain type of neovascularization. In the present study, we evaluated the difference in the treatment burden among different types of neovascularization. Furthermore, we focused on the treatment burden on one patient, not on one eye.

Methods

This retrospective, observational study was conducted at a single center (Kim's Eye Hospital, Seoul, South Korea). The study was approved by the Institutional Review Board of Kim's Eye Hospital and was conducted in accordance with the tenets of the Declaration of Helsinki.

Patients

The present study included patients who were first diagnosed with treatment-naïve neovascular AMD between January 2014 and December 2015. Additional inclusion criteria were (1) initially treated with three loading injections of anti-VEGF, and (2) followed up for at least 24 months after diagnosis. The exclusion criteria were (1) lack of indocyanine green angiography (ICGA) results or unable to differentiate subtypes of neovascularization, (2) end-stage diseases, such as extensive fibrotic scars involving the fovea or geographic atrophy (GA), and (3) received treatment during clinical trials for neovascular AMD or PCV.

Examinations

During diagnosis, the best-corrected visual acuity (BCVA) was measured, and images of the fundus were obtained using CX-1® (Topcon; Tokyo, Japan). Fluorescein angiography and ICGA images were acquired using combined confocal scanning laser ophthalmoscopy and spectral domain optical coherence tomography (OCT) (Spectralis HRA + OCT®; Heidelberg Engineering GmbH, Heidelberg, Germany). The OCT scans were acquired using the Spectralis HRA + OCT®, RS 3000® (Nidek Co., Ltd., Tokyo, Japan), or Spectral OCT® (Ophthalmic Technologies Inc., Toronto, Canada).

Type 3 neovascularization was diagnosed using multimodal imaging based on the previously suggested method [22]. The diagnosis of PCV was based on the presence of polypoidal lesions with or without branching vascular networks in ICGA images [14, 23]. For cases of submacular hemorrhage, in which the definite diagnosis of PCV was not possible using ICGA images obtained at the initial diagnosis, ICGA images were acquired within 3 months after the diagnosis was received.

Treatment and follow-up

The treatment and follow-up method used in this study were similar to those used in our previous study [24]. Patients were initially administered three monthly injections of either ranibizumab (0.5 mg/0.05 mL of Lucentis®; Genentech Inc., San Francisco, CA, USA) or aflibercept (2.0 mg/0.05 mL of Eylea®; Regeneron, Tarrytown, NY, USA). After the initial treatment, retreatment was performed on as-needed basis. Patients were followed up without additional treatment until the first reactivation.

During the first 12 months of follow-up, patients were scheduled to visit the hospital every 1–2 months, and follow-up interval was extended to 3 months at the physician's discretion. Subsequently, the follow-up interval was extended to 4 or 6 months. During the as-needed phase, additional anti-VEGF injections were administered if any of the following changes were noted: (1) OCT evidence of persistent fluid 1–

2 months after the previous injection; (2) reaccumulation of subretinal or intraretinal fluid involving the fovea or threatening to involve the fovea as visualized on OCT; and (3) new or increased retinal or subretinal hemorrhage on clinical examination. After a reinjection, the follow-up interval was shortened to 1–2 months.

If the treating physician determined that a more effective treatment was required to preserve vision, the treatment regimen was changed from the as-needed regimen to the proactive regimen after obtaining the patient's agreement. No guidelines for switching were established. During the proactive phase, the interval between injections was adjusted by 2–4 weeks, according to the physician's discretion. The maximum interval between injections was set as 3–4 months. When lesion reactivation was noted in bilateral eyes at a follow-up visit, bilateral eye injections were administered on the same day, or the other eye injection was administered within 1 week after the first eye injection. In some patients, the treatment was discontinued at the physician's discretion.

Outcome measures

The following data were collected: patient's age, sex, follow-up period, incidence of bilateral involvement of neovascularization during the follow-up period, type of anti-VEGF injections used for treatment, the number of hospital visits and anti-VEGF injections during the follow-up period, and the distance between the hospital and patient's residence. The number of hospital visits was counted only when patients visited the hospital for examination and/or treatment related to neovascular AMD. The distance between the hospital and patients' residence was defined as a straight-line distance between the address of our institution and the address of patients' residence. The distance was measured using the electronic caliper provided by Google Maps (Google Inc., Mountain View, CA, USA). If both eyes met the eligible criteria in a patient, anti-VEGF injections and the number of hospital visits for both eye treatments were summed up.

Based on the results of examinations at initial diagnosis, patients were divided into three groups (Fig. 1): (1) type 1 or 2 neovascularization group = type 1 or 2 neovascularization without PCV features on ICGA, (2) type 3 neovascularization group = patients diagnosed with type 3 neovascularization, and (3) PCV group = patients diagnosed with PCV. Baseline characteristics, including the age, sex, hypertension, diabetes mellitus, distance between the hospital and the patients' residence, and BCVA, were compared among the three groups. The number of hospital visits per year and the number of anti-VEGF injections per year were also compared among the three groups. The same comparison was performed between patients with unilateral disease and those with bilateral involvement. Moreover, the incidence of bilateral involvement was compared among the three groups.

Additional comparisons, including the degree of deterioration in BCVA between the diagnosis and the final follow-up, incidence of fovea-involving scars, and retinal pigment epithelial (RPE) atrophy, were performed among the three groups. In patients with bilateral involvement, only data from the first-involved eyes were included in this analysis. In patients with bilateral involvement, the number of same-day injections in bilateral eyes per year was compared among the three groups.

Statistical analyses

The data are presented as mean ± standard deviation or number (percentage), wherever applicable. The statistical analyses were performed using a commercially available software package (SPSS, version 12.0 for Windows; IBM Corporation, Armonk, NY, USA). Comparisons among the groups were performed using one-way analysis of variance with Tukey's test, independent samples *t* test, or chi-squared test. Multivariate analysis was performed using multiple linear regression. *P* values less than 0.05 were considered statistically significant.

Results

Among the 740 patients diagnosed with neovascular AMD during the study period and initially treated with three loading injections of anti-VEGF, 497 were followed up for at least 24 months. Among them, 66 were excluded from the study for the following reasons: lack of ICGA results or unable to differentiate subtypes of neovascularization (52 patients), end-stage diseases, such as extensive fibrotic scars involving the fovea or GA (6 patients), and received treatment during clinical trials for neovascular AMD or PCV (8 patients). Finally, 431 patients (271 men and 160 women) were included in the study.

The mean age was 69.6 ± 8.4 years, and mean follow-up period was 50.6 ± 11.3 months. One hundred sixty-seven patients (38.7%) were diagnosed as having type 1 or 2 neovascularization, 50 patients (11.6%) were diagnosed as having type 3 neovascularization, and 214 patients (49.7%) were diagnosed as having PCV. The mean distance between the hospital and patients' residence was 32.3 ± 64.4 km. Table 1 summarizes results of the comparison of baseline characteristics among three different subtypes of neovascularization. There was a significant difference in the age ($P < 0.001$) and sex ($P < 0.001$) among the three groups.

The mean number of hospital visits was 25.5 ± 8.0 and the mean number of anti-VEGF injections administered during the follow-up period was 10.0 ± 6.5; the anti-VEGF agents used during the follow-up period were ranibizumab alone (126 eyes), aflibercept alone (75 eyes), ranibizumab and

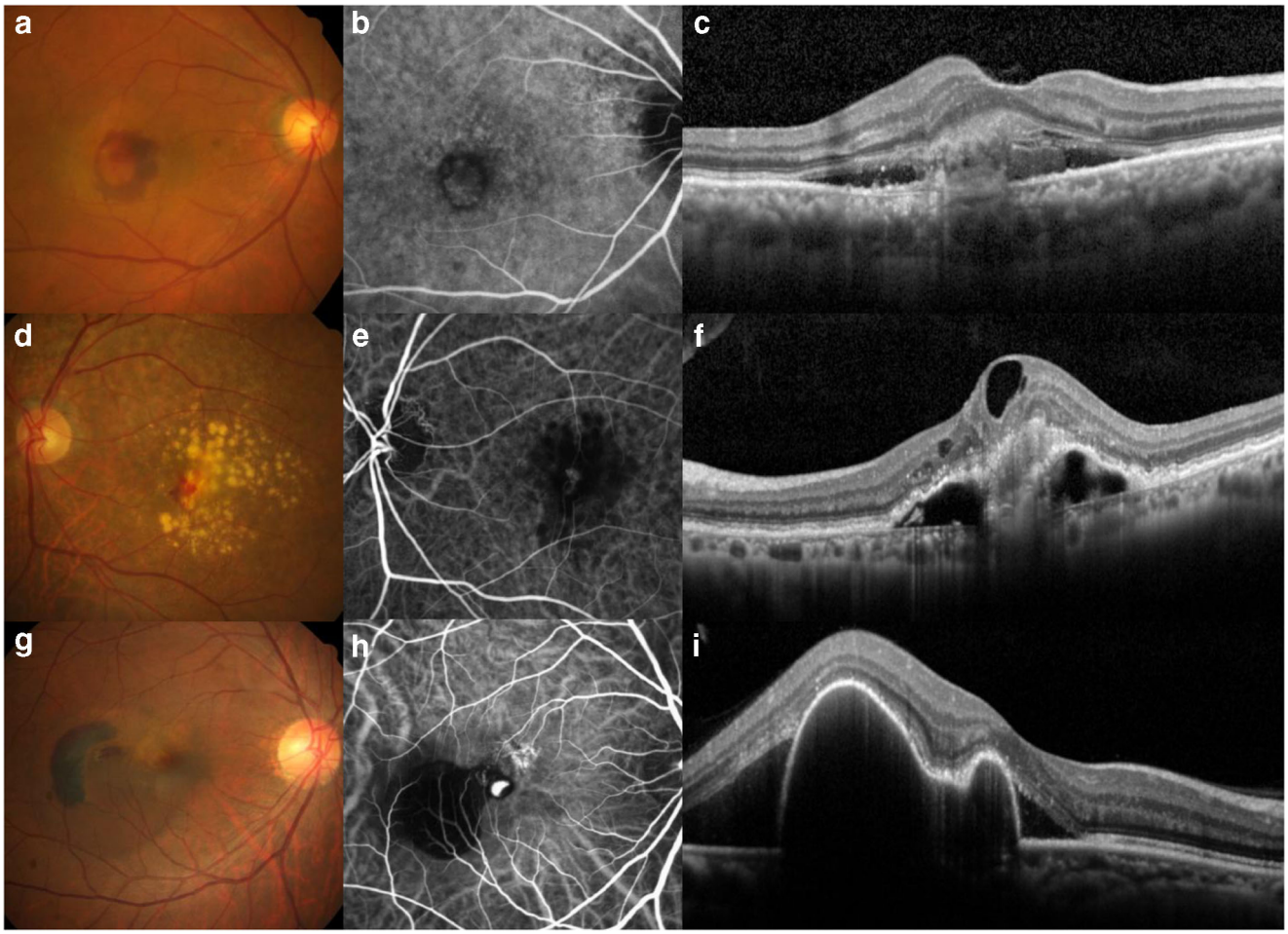

Fig. 1 Representative images of patients included in type 1 or 2 neovascularization group (**a**–**c**), type 3 neovascularization group (**d**–**f**), and polypoidal choroidal vasculopathy group (**g**–**h**). **a**, **d**, **g** fundus photography images; **b**, **e**, **h** indocyanine green angiography images; **c**, **f**, **i** optical coherence tomography images

bevacizumab (58 eyes), aflibercept and bevacizumab (44 eyes), ranibizumab and aflibercept (72 eyes), and ranibizumab, aflibercept, and bevacizumab (56 eyes). Among the 431 included patients, the treatment regimen was

Table 1 Comparison of baseline characteristics among three different subtypes of neovascularization

	Type 1 or 2 NV group ($n = 167$)	Type 3 NV group ($n = 50$)	PCV group ($n = 214$)	P value
Age, years	71.6 ± 7.5	75.1 ± 6.1	67.2 ± 8.1	< 0.001*
	A†	B†	C†	
Sex (men:women)	98 (58.7%):69 (41.3%)	10 (20.0%):40 (80.0%)	163 (76.2%):51 (23.8%)	< 0.001‡
Hypertension	88 (52.7%)	23 (46.0%)	97 (45.3%)	0.340‡
Diabetes mellitus	39 (23.4%)	14 (28.0%)	34 (15.9%)	0.068‡
Distance between the hospital and the patients' residence, km	37.1 ± 74.3	25.0 ± 47.5	30.2 ± 59.3	0.408*
	A†	A†	A†	
BCVA, logMAR	0.73 ± 0.49	0.66 ± 0.48	0.60 ± 0.48	0.056*
	A†	A†	A†	

NV neovascularization, *PCV* polypoidal choroidal vasculopathy, *BCVA* best-corrected visual acuity

*Statistical analysis was performed using the one-way analysis of variance. † Statistical analysis was performed using the one-way analysis of variance with Tukey's test. The same letter indicates a non-significant difference between the groups, whereas different letters indicate significant differences between the groups. ‡ Statistical analysis was performed using the chi-squared test

switched from as-needed to proactive in 53 (12.3%) at a mean duration of 30.5 ± 15.8 months after the diagnosis.

In all included eyes, the number of anti-VEGF injections during the first 12 months after the diagnosis was 4.7 ± 1.7. A mean number of 5.3 ± 5.5 injections was additionally administered between the 12-month and final follow-ups. In the type 1 or 2 neovascularization group, a mean number of 4.6 ± 1.7 injections was administered during the first 12 months, followed by 4.8 ± 5.5 injections between the 12-month and final follow-ups. In the PCV group, the values were 4.6 ± 1.7 and 5.1 ± 4.9, respectively. In the type 3 neovascularization group, the values were 5.2 ± 1.9 and 8.3 ± 7.1, respectively.

Table 2 summarizes the results of comparisons of the number of hospital visits per year and the number of anti-VEGF injections per year among three different subtypes of neovascularization. The number of hospital visits per year was significantly higher in the type 1 or 2 neovascularization group (mean 6.1 ± 1.5) and type 3 neovascularization group (mean 6.6 ± 1.6) than in the PCV group (mean 6.0 ± 1.5) ($P < 0.001$). The number of anti-VEGF injections per year was significantly higher in the type 3 neovascularization group (mean 3.1 ± 1.7) than in the type 1 or 2 neovascularization group (mean 2.3 ± 1.5) or the PCV group (mean 2.3 ± 1.2) ($P = 0.042$). Table 3 summarizes the number of hospital visits per year and number of anti-vascular endothelial growth factor injections per year in three different subtypes of neovascularization according to the anti-vascular endothelial growth factor agent used.

During the follow-up period, bilateral involvement was noted in 90 patients (20.9%). Among the 1233 injections administered in these 90 patients, 138 (69 for each eye) were administered on the same day. There was no difference in the number of same-day injections per year among the type 1 or 2 neovascularization (mean 1.7 ± 2.9), PCV (mean 1.7 ± 2.8), and type 3 neovascularization (mean 1.0 ± 1.9) groups ($P = 0.595$). The number of hospital visits per year was significantly higher in patients with bilateral involvement (6.9 ± 1.6) than in those without bilateral involvement (5.9 ± 1.5) ($P < 0.001$, Table 4). The number of anti-VEGF injections per year was also significantly higher in patients with bilateral involvement (3.3 ± 1.7) than in those without bilateral involvement (2.2 ± 1.3) ($P < 0.001$, Table 4). There was a significant difference in the incidence of bilateral involvement among type 1 or 2 neovascularization group (20.4%), type 3 neovascularization group (46.0%), and the PCV group (15.4%) ($P < 0.001$, Table 5).

The mean logMAR BCVA was 0.66 ± 0.48 at the diagnosis and 0.84 ± 0.74 at the final follow-up. The BCVAs at the diagnosis and final follow-up were 0.73 ± 0.49 and 1.01 ± 0.78, respectively, in the type 1 or 2 neovascularization group, 0.60 ± 0.48 and 0.61 ± 0.65, respectively, in the PCV group, and 0.66 ± 0.48 and 0.84 ± 0.74, respectively, in the type 3 neovascularization group. The degree of deterioration in BCVA was significantly greater in the type 3 neovascularization group than in the type 1 or 2 neovascularization ($P = 0.047$) or PCV ($P < 0.001$) group. The degree of deterioration in BCVA was significantly greater in the type 1 or 2 neovascularization group than in the PCV group ($P < 0.001$). The incidence of fovea-involving scars was 34.7% (58 of 167) in the type 1 or 2 neovascularization group, 15.4% (33 of 214) in the PCV group, and 36.0% (18 of 50) in the type 3 neovascularization group. There was a significant difference in the incidence of scars among the three groups ($P < 0.001$). The incidence of fovea-involving RPE atrophy was 14.4% (24 of 167) in the type 1 or 2 neovascularization group, 6.1% (13 of 214) in the PCV group, and 28.0% (14 of 50) in the type 3 neovascularization group. There was a significant difference in the incidence of RPE atrophy among the three groups ($P < 0.001$).

Discussion

The frequency of hospital visits and that of anti-VEGF injections are major contributors to patients' treatment burden. The as-needed treatment regimen was introduced to reduce the frequency of injections [25]. In addition, one of the major reasons for developing treat-and-extend regimen was to

Table 2 Comparison of the number of hospital visits per year and the number of anti-vascular endothelial growth factor injections per year among three different subtypes of neovascularization

	Type 1 or 2 NV group ($n = 167$)	Type 3 NV group ($n = 50$)	PCV group ($n = 214$)	P value
No. of hospital visits per year	6.1 ± 1.5	6.6 ± 1.6	6.0 ± 1.5	< 0.001*
	A†	A†	B†	
No. of anti-VEGF injections per year	2.3 ± 1.5	3.1 ± 1.7	2.3 ± 1.2	0.042*
	A†	B†	A†	

* Statistical analysis was performed using one-way analysis of variance. † Statistical analysis was performed using the one-way analysis of variance with Tukey's test. The same letter indicates a non-significant difference between the groups, whereas different letters indicate significant differences between the groups. *NV*, neovascularization; *PCV*, polypoidal choroidal vasculopathy; *VEGF*, vascular endothelial growth factor

Table 3 Number of hospital visits per year and number of anti-vascular endothelial growth factor injections per year in three different subtypes of neovascularization, according to the anti-vascular endothelial growth factor agent used

Anti-VEGF agent used	Type 1 or 2 NV group	Type 3 NV group	PCV group
Ranibizumab alone	($n = 60$)	($n = 13$)	($n = 53$)
No. of hospital visits per year	5.5 ± 1.5	5.8 ± 0.8	5.2 ± 1.3
No. of anti-VEGF injections per year	1.5 ± 1.1	1.8 ± 0.9	1.4 ± 0.8
Aflibercept alone	($n = 22$)	($n = 7$)	($n = 46$)
No. of hospital visits per year	6.4 ± 1.6	5.4 ± 1.2	5.6 ± 1.4
No. of anti-VEGF injections per year	2.2 ± 1.5	1.5 ± 0.8	1.8 ± 1.0
Ranibizumab and bevacizumab	($n = 26$)	($n = 14$)	($n = 18$)
No. of hospital visits per year	6.3 ± 1.5	7.2 ± 1.6	5.5 ± 1.5
No. of anti-VEGF injections per year	2.3 ± 1.4	4.1 ± 1.3	2.0 ± 0.9
Aflibercept and bevacizumab	($n = 19$)	($n = 5$)	($n = 20$)
No. of hospital visits per year	6.2 ± 1.5	5.7 ± 1.6	6.2 ± 1.4
No. of anti-VEGF injections per year	2.6 ± 1.2	3.5 ± 1.8	3.1 ± 1.2
Ranibizumab and aflibercept	($n = 20$)	($n = 2$)	($n = 50$)
No. of hospital visits per year	6.6 ± 1.6	7.4 ± 0.7	6.8 ± 1.5
No. of anti-VEGF injections per year	2.3 ± 1.2	3.3 ± 1.5	3.0 ± 1.2
Ranibizumab, aflibercept, and bevacizumab	($n = 20$)	($n = 9$)	($n = 27$)
No. of hospital visits per year	6.8 ± 1.1	8.3 ± 1.2	6.9 ± 1.1
No. of anti-VEGF injections per year	4.2 ± 1.6	4.6 ± 1.3	3.3 ± 0.9

NV neovascularization, *PCV* polypoidal choroidal vasculopathy, *VEGF* vascular endothelial growth factor

reduce the number of hospital visits [26]. In the present study, we focused on these two factors.

In a study conducted by Prenner et al. [27], patients with neovascular AMD reported an average time of 12 h per hospital visit. In addition, approximately half of the caregivers took time off their work and personal activities to provide transportation to patients' having appointments for treatment [27]. As caregivers often assist patients undergoing treatment for neovascular AMD, long-term treatment exerts a significant burden on them [28]. In the present study, the mean distance between the hospital and the patients' residence was 32.3 km, suggesting that patients had to travel a total mean distance of 64.6 km for AMD treatment. However, this was a straight-line distance, and the actual distance traveled by patients could be longer than the measured distance. In addition, depending on the transport system patients used and traffic situation, the time burden and travel fatigue can be considerably high despite a short travel distance. In this study, all patients were from South Korea, which is a small country with a total land area of only 100,295 km^2. Thus, the travel distance may increase if a similar analysis is performed in a larger country.

Although the patients were willing to accept long periods of waiting, as well as long treatment duration and traveling time to prevent deterioration of vision [29], regular anti-VEGF therapy can be financially burdening on them because of its high cost [30]. From a socio-economic perspective, anti-VEGF therapy is considered to be cost-effective and beneficial to the society [31, 32]. However, this does not reduce the financial burden on the patients. In addition, the burden varies significantly among patients depending on the frequency of injections required [25, 33], and the difference in the risk of bilateral involvement [34]. Some patients may experience tremendous financial burden. Moreover, the process of intraocular injection may cause anxiety [35] and pain [36, 37], especially in treatment-naïve patients, further adding to their burden.

In this study, we observed a significant difference in the frequency of hospital visits and that of anti-VEGF injections among different types of neovascularization.

Table 4 Comparison of the number of hospital visits per year and the number of anti-vascular endothelial growth factor injections per year between patients with and without bilateral involvement

	Bilateral involvement (+) ($n = 90$)	Bilateral involvement (−) ($n = 341$)	*P* value
No. of hospital visits per year	6.9 ± 1.6	5.9 ± 1.5	< 0.001*
No. of anti-VEGF injections per year	3.3 ± 1.7	2.2 ± 1.3	< 0.001*

VEGF vascular endothelial growth factor

*Statistical analysis was performed using independent samples *t* test

Table 5 Comparison of incidence of bilateral involvement among different subtypes of neovascularization

Type of neovascularization	Bilateral involvement (+)	Bilateral involvement (−)	*P* value
Type 1 or 2 NV group ($n = 167$)	34 (20.4%)	133 (79.6%)	< 0.001*
Type 3 NV group ($n = 50$)	23 (46.0%)	27 (54.0%)	
PCV group ($n = 214$)	33 (15.4%)	181 (84.6%)	

NV neovascularization, *PCV* polypoidal choroidal vasculopathy

*Statistical analysis was performed using chi-squared test

In particular, the frequencies were relatively higher in patients diagnosed with type 3 neovascularization than in those diagnosed with other subtypes of neovascularization. Type 3 neovascularization responded well to the anti-VEGF therapy. In previous studies, the number of injections required to treat type 3 neovascularization was comparable to that required to treat other subtypes of neovascular AMD [13, 38, 39]. Thus, high treatment burden of type 3 neovascularization may not be associated with the treatment response.

We believe that the primary reason of this observation in our patients was that the treatment burden was assessed per patient, not per eye. When both eyes were affected, the burden to treat both eyes was summed up. Moreover, high risk of bilateral involvement is a well-known characteristic of type 3 neovascularization [40]. For example, in an earlier study, Yannuzzi et al. [8] reported 24.1% of patients (26 of 108 patients) to have bilateral neovascularization. In addition, the incidence of fellow-eye neovascularization was reported to be between 38.3 and 100% in initial unilateral type 3 neovascularization during the follow-up period (mean: 27.8–36 months) [19, 21]. In this study, the frequency of hospital visits and that of anti-VEGF injections were significantly higher in patients with bilateral involvement than in those without it. Furthermore, the incidence of bilateral involvement was the highest in patients with type 3 neovascularization, suggesting it to be the primary reason for high treatment burden in these patients.

We believe high treatment burden in type 3 neovascularization is an interpretable result. Type 3 neovascularization usually develops in elderly patients [10]. Deterioration of vision in elderly patients can severely affect their lives, from causing discomfort to worsening the quality of life. For instance, it is reported that visual deterioration can increase the risk of falling and sustaining fractures [41]. Furthermore, restriction of physical activity owing to fracture can increase the risk of death by infection [42]. Therefore, preserving the vision in elderly patients requires active treatment accompanied with frequent visits to the hospital [43, 44], which increases the treatment burden. Although the burden is distributed and reduced with the involvement of a caregiver, it eventually increases the societal cost, apart from increasing the patient's burden.

Patients with type 3 neovascularization are at a high risk of bilateral vision loss. In addition to fellow-eye neovascularization [19, 21], the incidence of fellow-eye GA is high in patients with unilateral type 3 neovascularization [45]. As a result, the visual acuity of the better-seeing fellow eye at diagnosis could deteriorate during treatment. In some patients, the better-seeing eye at diagnosis changed to worse-seeing eye [45]. The vision in the better-seeing eye was closely associated with the quality of life [46]. In addition, societal costs dramatically increased as the vision in the better-seeing eye decreased [47]. Thus, preserving the vision of the initially involved eye is especially important in type 3 neovascularization. The lack of a proper treatment because of patients' inability to afford it may cause treatment discontinuation or treatment failure, which eventually increases the societal cost dramatically. The high frequency of hospital visits and that of anti-VEGF injections in patients diagnosed with type 3 neovascularization suggest high treatment burden. Therefore, more intense health/insurance supporting policies, including more financial support, are required for patients with type 3 neovascularization.

In addition, efficient treatment strategies can be useful for reducing the treatment burden. Several previous studies provided clues for planning the efficient treatment. Some type 3 neovascularization cases did not reactivate after the initial loading injections [48]. Based on this observation, we postulated that proactive treatment, such as the treat-and-extend regimen, may not be necessary for cases without reactivation. Although the treat-and-extend regimen is effective in treating neovascular AMD, it usually requires more frequent injections compared to the as-needed regimen. In addition, it may lead to redundant injections for patients without long-term reactivation [49]. Using the as-needed regimen at least in the first year for patients with type 3 neovascularization may reduce the treatment burden by reducing the number of injections. This approach can also help identify patients without long-term reactivation. However, considering more stable visual outcomes of the treat-and-extend regimen compared to the as-needed regimen [50, 51], switching to the treat-and-extend regimen after the first reactivation would be plausible. The first reactivation after the initial loading injection is usually noted within 15 months in type 3 neovascularization [48]. When using the as-needed regimen, monthly monitoring visits are usually recommended for the prompt detection of lesion reactivation. However, to reduce the burden of hospital visits,

the interval between monitoring visits can be extended after 15 months for patients without reactivation.

Several previous studies demonstrated decreased lesion reactivations in type 3 neovascularization when retinal pigment epithelial (RPE) atrophy developed and progressed [24, 52]. Therefore, a more efficient treatment could be applied for patients with progression of RPE atrophy; the injection frequency can be reduced, or interval between hospital visits can be elongated. To date, no specific guidelines on how to apply the aforementioned findings to clinical practice have been established. Further studies are required to establish efficient treatment guidelines for patients showing RPE atrophy without compromising the treatment efficacy.

When using the treat-and-extend regimen, the maximum interval between injections can influence the injection frequency. Although several studies evaluated the outcomes of the treat-and-extend regimen in type 3 neovascularization, the maximum interval between injections had been set as 12 weeks in those studies [53, 54]. Recent evidence suggests that the treat-and-extend regimen can be effectively applied even with maximum injection intervals of 16 weeks [55]. Further studies are required to identify whether or not the protocol of a 16-week interval can be applied to type 3 neovascularization for a more efficient treatment.

In the present study, neovascular AMD was classified using the arbitrary criteria: type 3 neovascularization was categorized under a separate group, whereas both types 1 and 2 neovascularization were categorized under one group. Type 3 neovascularization is a distinct entity with characteristic features distinguishable from other types of neovascularization. Although features of types 1 and 2 neovascularization differ, their differences from those of type 3 neovascularization may be greater. In addition, when types 1 and 2 neovascularization are separately analyzed, a total of four neovascularization groups are compared. This may impede the accurate statistical analysis by further reducing the number of patients in each group. As a result, only type 3 neovascularization was categorized under a separate group. Using the arbitrary criteria for the neovascular AMD classification was a limitation of the study.

With increase in the number of patients receiving active treatment for neovascular AMD [5, 56], more individualized care strategies will be required in the future. This care would not only be confined to treatment and follow-up methods but also need to include social support systems for patients. We believe that results of this study will contribute to the development of such support systems. In addition, our results may be useful when discussing the future treatment strategy with patients and their caregivers.

The strength of this study is that we focused on the difference in the treatment burden among different types of neovascularization. In addition, treatment burden was evaluated in one patient, not one eye. However, this study also has several limitations. First, this study was retrospectively performed in a single institution. Second, retreatment of patients was largely based on as-needed regimen and follow-up intervals were not strictly controlled. Compared to the previous real-world outcome study by Holz et al. [38], the number of hospital visits and that of anti-VEGF injections in our patients were relatively comparable to those reported in Italy. This decrease in the number of frequent hospital visits and that of anti-VEGF injections suggests that some patients in our study may have been undertreated. Third, when collecting patients' address data, it was not possible to identify whether the patient had moved. Fourth, the small sample size of the type 3 neovascularization group may lead to an error in the statistical analysis. Fifth, the usage of an anti-VEGF agent was uncontrolled. Thus, the difference in the efficacy among the anti-VEGF agents may have influenced the study results. Sixth, although statistical significance was not reached, the distance between the hospital and the patients' residence was relatively shorter in the type 3 neovascularization group than in other subtypes of neovascularization. This short distance may have influenced the more frequent hospital visits in the type 3 neovascularization group. Lastly, all included patients were Korean. Because treatment methods and outcomes may be affected by policies of national health and insurance or insurance companies, it may be difficult to directly apply the study results to other countries. Thus, further studies are required to identify whether similar trends are noted in other countries.

As this study was performed using the data obtained from clinical setting, study results may not reflect the most effective, standard treatment. Nevertheless, the real-world data may have its value [57], especially when randomized controlled trials have not yet been performed on a similar disease area.

In conclusion, the frequency of hospital visits and that of anti-VEGF injections in patients with type 3 neovascularization was higher than in those with other types of neovascularization. High incidence of bilateral involvement in patients with type 3 neovascularization could have contributed to this difference. These results suggest high treatment burden on patients with type 3 neovascularization and the need for better support systems for these patients. Because we primarily used as-needed basis retreatment modality in our patients, further studies are required to identify whether different results are obtained if the treat-and-extend based retreatment strategy is used.

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Compliance with ethical standards

Conflict of interest Jae Hui Kim: advisory board of Bayer and Novartis. The following authors have no financial disclosure: Ji Hyun Lee, Jong Woo Kim, Chul Gu Kim, Dong Won Lee.

Ethical approval The study was approved by the institutional review board of Kim's Eye Hospital (Seoul, South Korea). This study was conducted in accordance with the tenets of the Declaration of Helsinki.

Informed consent Informed consent was not obtained in this study. Identifying information about participants was not presented in this study.

Proprietary interest or competing interest None.

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