Real-world Changes in Injection Frequency and Visual Outcomes Over Time in the Treatment of Neovascular Age-related Macular Degeneration

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Abstract

BACKGROUND: To evaluate time-dependent changes in injection frequency and visual outcome for the treatment of neovascular age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV).

METHODS: This retrospective study included 667 patients (667 eyes) diagnosed with treatment-naïve neovascular AMD and PCV in 2013 (2013 group), 2015 (2015 group), 2017 (2017 group), and 2019 (2019 group). The number of anti-vascular endothelial growth factor (VEGF) injections and degrees of changes in visual acuity during the first 24 months after diagnosis were compared among the four time groups.

RESULTS: During 24 months, the 2013, 2015, 2017, and 2019 groups received means of 5.7 ± 2.7, 6.0 ± 2.8, 6.6 ± 3.0, and 6.9 ± 3.3 injections anti-VEGF injections, respectively. The number of injections was significantly higher in the 2019 group than in the 2013 and 2015 groups (P = 0.003). The mean degree of visual change during the 24 months follow-up period was 0.07 ± 0.55 deterioration in the 2013 group, 0.01 ± 0.51 deterioration in the 2015 group, 0.08 ± 0.50 improvement in the 2017 group, and 0.04 ± 0.48 improvement in the 2019 group. There was a significant difference in the degree of visual changes among the four groups (P = 0.020).

CONCLUSION: There was a trend of increasing injection frequency over time and the visual outcome was relatively better in patients diagnosed in the later period. This trend should be considered when predicting the future socioeconomic burden of neovascular AMD and PCV.

Introduction

Neovascular age-related macular degeneration (AMD) is one of the main global causes of vision loss.[1] With the advent of anti-vascular endothelial growth factor (VEGF) therapy, the treatment outcome of neovascular AMD has markedly improved.[2,3] However, the cost of anti-VEGF drugs and frequent hospital visits place a tremendous burden on patients. Therefore, more efficient treatment regimens have been developed.

The as-needed regimen was the first widely used regimen for efficient anti-VEGF treatment for neovascular AMD.[4] Compared to the fixed-dosing regimen, the as-needed regimen showed similar efficacy with a low injection frequency.[4] However, to achieve good treatment outcomes, monthly follow-up should be performed, with re-injection based on the detailed re-injection criteria.[4] In the clinical setting, however, this strict follow-up and injection cannot be performed in many patients.[5,6] As a result, real-world patients are generally undertreated[5–7] and the visual outcome is markedly unfavorable compared to that reported in clinical trials.[5,6]

The treat-and-extend (TAE) regimen was introduced for efficient treatment years after the as-needed regimen.[8,9] Unlike the as-needed regimen, the TAE regimen can also reduce the number of hospital visits

for injections.[8,9] In addition, Spaide suggested that it is more convenient to make treatment decisions when using the TAE regimen compared to the as-needed regimen.[10] The efficacy of the TAE regimen is generally comparable to that of the fixed-dosing regimen and superior to that of the as-needed regimen.[11,12] In addition, switching from the as-needed regimen to the TAE regimen leads to improvement or at least stabilization of visual outcome.[13,14] However, the TAE regimen generally requires more frequent injections than those in the as-needed regimen.[11,13] Thus, while the TAE regimen may lead to improved treatment outcomes, the injection frequency is higher in real-world practice.

More than 15 years have passed since the introduction of anti-VEGF therapies. During this period, physicians' practice patterns may have changed. The clinical experiences of each physician, along with additional study results, might have influenced this change. With the increasing prevalence of AMD[15] accompanied by an increasing number of patients undergoing long-term active treatment,[16] the treatment burden of neovascular AMD may arise as a major future global health issue. Thus, investigating the changes in the trends of neovascular AMD treatment is of great value.

The present study evaluated the time-dependent changes in injection frequency and visual outcome for the treatment of neovascular AMD and polypoidal choroidal vasculopathy (PCV) based on real-world data.

Materials And Methods

This retrospective study was conducted in 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. Due to the retrospective nature of this study, the need for an informed consent was waived off (Kim's Eye Hospital IRB, Seoul, South Korea).

Patients

We secured the list of patients who were diagnosed with treatment-naïve neovascular AMD and PCV in our institution in 2013, 2015, 2017, and 2019, based on fluorescein angiography, indocyanine green angiography (ICGA), and optical coherence tomography (OCT) examinations. Patients initially treated with three monthly loading injections of ranibizumab or aflibercept were included. The exclusion criteria were 1) loss to follow-up before 24 months; 2) history of vitreoretinal surgery; 3) patients who underwent photodynamic therapy or glaucoma surgery; and 4) patients who participated in any clinical trial during the study period. When both eyes met the eligibility criteria, those that received anti-VEGF injections first were included in the study.

Treatment and follow-up

Patients were initially administered three monthly injections of 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, re-treatment was generally performed according to as-

needed regimens using one of three anti-VEGF agents—ranibizumab, aflibercept, or bevacizumab (1.25 mg/0.05 mL of Avastin™; Genentech Inc). In patients treated using the as-needed regimen, the treatment regimen was changed to the TAE regimen when the treating physician determined that a more effective treatment was required to preserve vision. Treatment was discontinued at the physician's discretion in some patients with profound vision loss. Ranibizumab and bevacizumab were introduced before the study period, whereas aflibercept was first introduced in May 2014. The as-needed regimen was introduced before the study period, whereas the TAE regimen was first introduced in 2015.

In the present study, the TAE regimen was slightly modified from its original version.[14] Injections were performed at an initial interval of 4–8 weeks. Subsequently, the interval was extended or shortened by 2–3 weeks in the absence or presence of fluid or hemorrhage, respectively. The maximum interval between injections was determined on an individual basis. For patients who expressed anxiety regarding lesion re-activation and the need for more effective treatment, the maximum interval between injections was set to 12 weeks; for those who wanted a more efficient treatment without frequent injections, the interval was set to 16 weeks.

Outcome analyses

The patients were divided into four time groups according to the year in which they were diagnosed with neovascular AMD or PCV (2013, 2015, 2017, or 2019). The baseline characteristics, including patient age, sex, type of macular neovascularization (MNV)(type 1 or 2 MNV *vs.* type 3 MNV *vs.* PCV), best-corrected visual acuity (BCVA), and type of anti-VEGF agent (ranibizumab *vs.* aflibercept) used for initial loading injections were compared among the four groups. The following parameters were also compared among the four groups: 1) the number of anti-VEGF injections during the 24-month follow-up period, 2) the proportion of patients treated using the TAE regimen, 3) the changes in BCVA between diagnosis and 24 months, and 4) the proportion of patients exhibiting ≥ 2 lines of visual deterioration between 3 and 24 months.

When the patient did not report for follow-up exactly 24 months after diagnosis, the BCVA values measured at the closest hospital visit to the 24 months were used for analysis. Patients who were treated using the TAE regimen immediately after receiving the initial loading injection and patients who were initially treated using the as-needed regimen but switched to the TAE regimen during the follow-up were categorized as received the TAE regimen. The proportions of patients treated under the TAE regimen were compared between the 2013, 2015, 2017, and 2019 groups. The numbers of injections during the 24 months were also compared between patients with and without the TAE regimen.

The patients were also divided into four groups according to the MNV type (type 1 or 2 MNV, type 3 MNV, and PCV), among which and the numbers of anti-VEGF injections were compared.

Statistical analysis

Data are presented as means ± standard deviation or numbers (%), where applicable. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

Comparisons between parameters among different groups were performed using chi-square tests with and without linear by linear regression, Fisher's exact tests, and one-way analysis of variance with Tukey's tests. Statistical significance was set at $P < 0.05$.

Results

During the study period, 1370 patients were diagnosed with treatment-naïve neovascular AMD and PCV and received three loading injections of anti-VEGF. Among them, 444 (32.4%) patients were excluded for 1) loss to follow-up before 24 months (416 patients), 2) history of vitreoretinal surgery or glaucoma surgery (12 patients), 3) patients who underwent photodynamic therapy (3 patients), and 4) patients who participated in any clinical trial during the study period (13 patients). As a result, 926 patients (926 eyes) were ultimately included in the analysis.

The 2013, 2015, 2017, and 2019 groups included 179 (19.3%), 235 (25.4%), 253 (27.3%), and 259 (27.9%) patients, respectively. The results of comparisons of baseline characteristics among these groups are summarized in Table 1.

Table 1
Comparison of baseline characteristics among the 2013, 2015, 2017, and 2019 groups.

Characteristics	2013 group (n = 179)	2015 group (n = 235)	2017 group (n = 253)	2019 group (n = 259)	P-value
Age, years	69.3 ± 9.0	69.9 ± 8.4	70.5 ± 8.4	70.4 ± 8.0	0.449*
Sex					0.023†
Male	120 (67.1%)	150 (63.8%)	146 (57.7%)	140 (54.1%)	
Female	59 (32.9%)	85 (36.2%)	107 (42.3%)	119 (45.9%)	
Type of neovascularization					< 0.001†
Type 1 or 2 MNV	58 (32.4%)	94 (40.0%)	124 (49.0%)	133 (51.4%)	
Type 3 MNV	24 (13.4%)	21 (8.9%)	26 (10.3%)	34 (13.1%)	
PCV	97 (54.2%)	120 (51.1%)	103 (40.7%)	92 (35.5%)	
Best-corrected visual acuity, logMAR	0.67 ± 0.52	0.62 ± 0.45	0.57 ± 0.48	0.58 ± 0.51	0.124*
Anti-VEGF agent used for loading injections					< 0.001†
Ranibizumab	179 (100.0%)	165 (70.2%)	94 (37.2%)	101 (38.9%)	
Aflibercept	0	70 (29.8%)	159 (62.8%)	158 (61.0%)	
* One-way analysis of variance					
†: Chi-square test					
MNV = macular neovascularization, PCV = polypoidal choroidal vasculopathy, logMAR = logarithm of minimal angle of resolution, VEGF = vascular endothelial growth factor					

There were significant differences in the MNV type (P = < 0.001) and anti-VEGF agent used for loading injections (P < 0.001) among the four groups. During 24 months, the 2013, 2015, 2017, and 2019 groups received means of 5.7 ± 2.7, 6.0 ± 2.8, and 6.6 ± 3.0, and 6.9 ± 3.3 anti-VEGF injections, respectively (Table 2).

Table 2
Comparison of the numbers of anti-vascular endothelial growth factor injections among the 2013, 2015, 2017, and 2019 groups.

Characteristics	2013 group (n = 179)	2015 group (n = 235)	2017 group (n = 253)	2019 group (n = 259)	P-value
Ranibizumab	5.1 ± 2.3	3.6 ± 2.9	2.1 ± 2.9	2.1 ± 3.7	
Aflibercept	0.2 ± 0.7	2.3 ± 2.9	4.0 ± 3.4	3.9 ± 3.6	
Bevacizumab	0.4 ± 1.2	0.1 ± 0.5	0.5 ± 1.3	0.9 ± 1.7	
No. of total anti-VEGF injections	5.7 ± 2.7	6.0 ± 2.8	6.6 ± 3.0	6.9 ± 3.3	< 0.001*
Use of TAE regimen	-	17 (7.2%)	23 (9.1%)	35 (13.5%)	< 0.001†
* Statistical analysis was performed using one-way analysis of variance					
†: Statistical analysis was performed using chi-square test with linear by linear regression VEGF = vascular endothelial growth factor, TAE = treat-and-extend					

There was a significant difference in the number of injections among the four groups (P < 0.001). The number of injections was significantly higher in the 2019 group than in the 2013 (P < 0.001) and 2015 groups (P = 0.013). The number of injections in the 2017 group was also significantly higher than that in the 2013 group (P = 0.003).

In type 1 or 2 MNV, 2013 (n = 58), 2015 (n = 94), 2017 (n = 124), and 2019 (n = 133) groups received means of 5.6 ± 2.8, 6.0 ± 2.9, 6.7 ± 3.1, and 6.9 ± 3.4 injections. In type 3 MNV, the 2013 (n = 24), 2015 (n = 21), 2017 (n = 26), and 2019 (n = 34) groups received means of 5.9 ± 2.5, 6.2 ± 2.9, 7.2 ± 3.4, and 8.2 ± 3.7 injections, respectively. In PCV, the values were 5.6 ± 2.7 in the 2013 group (n = 97), 6.0 ± 2.7 in the 2015 group (n = 120), 6.2 ± 2.8 in the 2017 group (n = 103), and 6.3 ± 3.0 in the 2019 group (n = 92).

None of the patients in the 2013 group received treatment based on the TAE regimen, while 17 (7.2%), 23 (9.1%), and 35 (13.5%) patients in the 2015, 2017, and 2019 groups, respectively, received this regimen. There was an increasing trend in the proportion of patients using the TAE regimen over time (P < 0.001). Among the 75 patients treated using the TAE regimen, the number of injections in patients treated using the TAE regimen (mean 10.5 ± 2.9) was significantly higher than that in patients treated using the as-needed regimen throughout the follow-up period (mean 5.9 ± 2.8)(P < 0.001).

In type 1 or 2 MNV, the mean number of anti-VEGF injections was 6.5 ± 3.1, while those for type 3 MNV and PCV were 7.0 ± 3.3 and 6.0 ± 2.8, respectively. There was a significant difference in the number of injections among the three groups (P = 0.005). The number was significantly higher for type 3 MNV than for PCV (P = 0.007).

In the 2013 group, the mean BCVA was 0.68 ± 0.52 at diagnosis 0.75 ± 0.67 at the final follow-up. In the 2015 group, the values were 0.62 ± 0.45 and 0.63 ± 0.59, respectively. In the 2017 group, the values were 0.57 ± 0.48 and 0.49 ± 0.47, respectively. In the 2019 group, the values were 0.58 ± 0.51 and 0.56 ± 0.60, respectively. The mean degrees of visual change during the 24-month follow-up period were 0.07 ± 0.55 deterioration in the 2013 group, 0.01 ± 0.51 deterioration in the 2015 group, 0.08 ± 0.50 improvement in the 2017 group, and 0.04 ± 0.48 improvement in the 2019 group. There was a significant difference in the degree of visual changes between the 2013 and 2017 groups (P = 0.014).

Discussion

The as-needed regimen is an efficient and effective treatment method for neovascular AMD. In the Early Treatment of Diabetic Retinopathy Study (ETDRS), Lalwani et al. reported a mean of 11.1 letters of visual improvement and a mean of 9.9 ranibizumab injections over 24 months.[17] In the Comparison of AMD Treatment Trials (CATT), a mean of 5.0 to 6.7 letters of improvement in visual acuity was noted at 24 months, with a mean of 12.6 to 14.1 injections of ranibizumab or bevacizumab.[18] Unlike the favorable outcomes in clinical trials,[17,18] however, treatment outcomes in real-world settings were generally unfavorable, with initially improved visual acuity continuously deteriorating over time.[5,6]

Holz et al. reported marked differences in real-world visual outcomes between European countries.[5] Their further analysis of the key drivers of visual acuity gains revealed that more frequent visits and injections were associated with greater improvements in visual acuity.[19] Patients from the United Kingdom (UK) showed the best visual outcome (4.1 letters of improvement), whereas those from Italy showed the worst visual outcome (2.9 letters of deterioration).[5] The mean number of hospital visits during 24 months was relatively higher in the UK (18.4) than that in Italy (12.7). In addition, the mean number of anti-VEGF injections was also relatively higher in the UK (9.0) than that in Italy (5.4).[11] These findings suggest that the unfavorable real-world treatment outcomes compared to those in clinical trials may be primarily derived from the less frequent hospital visits and subsequently fewer anti-VEGF injections. Spaide also recently confirmed the association between higher injection frequency and better visual outcome.[12]

The primary finding of the present study was the higher injection frequency in patients diagnosed in the later period. This trend was observed regardless of the MNV type. We postulate that the evidence demonstrated in previous studies[5,19] influenced the treatment patterns of doctors in our institution, subsequently leading to the observed trend. In addition, in recent years, the number of insurance-covered injections has increased in South Korea, reducing the economic burden on patients undergoing multiple injections.[10] This policy change may also have accelerated the observed trend. Thus, the treatment outcome was relatively better in patients diagnosed in the later period, supporting the findings of Holz et al.[19] and Spaide.[12]

In the present study, the number of injections was markedly higher in patients treated using the TAE regimen (mean 10.5) than that in patients treated using the as-needed regimen (mean 5.9). This result is

consistent with those of previous studies showing higher injection frequencies for the TAE regimen compared to the as-needed regimen. The higher use of the TAE regimen in patients treated in the later period may have contributed to the increased injection frequency in those patients.

The trend of increased injection frequency in the present study may suggest the future of neovascular AMD and PCV treatment. A further increase in injection frequency with wider use of the TAE regimen may result in better treatment outcomes, which may contribute to an increase in the patient population undergoing long-term active treatment without blindness. A reduction in drug cost by the introduction of anti-VEGF biosimilars[20] may facilitate this process. Further studies with discussions among experts are required to establish management plans for increasing socioeconomic burden, as well as increasing the size of the patient population undergoing active treatment.

In the present study, there was a difference in the proportions of anti-VEGF agents used for loading injections among the four time groups. We believe that this difference was primarily caused by the late introduction of aflibercept in South Korea. In general, aflibercept has a longer duration of action than that of ranibizumab, suggesting that the use of aflibercept may reduce the injection frequency.[21] Thus, the higher injection frequency in the 2017 group despite the higher use of aflibercept in this period highlights the tendency of increasing injection frequency over time.

The present study has limitations. First, this retrospective study was performed at a single institution. We did not control for treatment and follow-up schedules; thus, many of our patients may have been undertreated. Second, we excluded 32.4% of the patients for various reasons, suggesting that selection bias may have influenced the study results. Third, three different anti-VEGF drugs were used. There were no remarkable reported differences in visual outcomes among the three anti-VEGF agents.[18,22] However, these agents have different pharmacokinetics[23] and the influence of the mixed use of different anti-VEGF agents on the study results cannot be ignored. Fourth, all included patients were Korean. PCV is a prevalent MNV subtype in Asians. In addition, the use of anti-VEGF agents can be influenced by the health insurance system of the country. Thus, our results may not be directly applicable to other countries or ethnic groups. In fact, the study in Sweden by Schroder et al. observed no improvements in injection frequency or visual outcome with time.[24]

In summary, our evaluation of the time-dependent changes in treatment pattern and number of anti-VEGF injections for the treatment of neovascular AMD and PCV showed a trend of increasing injection frequency over time, resulting in better visual outcomes. This trend should be considered when predicting the future socioeconomic burden of these disorders.

Declarations

Data Availability.

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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b. Competing interest:

The authors declare no competing interests.

c. Author contributions:

Involved in conception and design (J.H.K.); acquisition of data (K.H.K., J.H.K., C.G.K., J.W.K.); analysis and interpretation (K.H.K., J.H.K., C.G.K., J.W.K.); drafting the article (K.H.K., J.H.K.); revising the article critically for important intellectual content (J.H.K); final approval of the article (K.H.K., J.H.K., C.G.K., J.W.K.).

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Figures

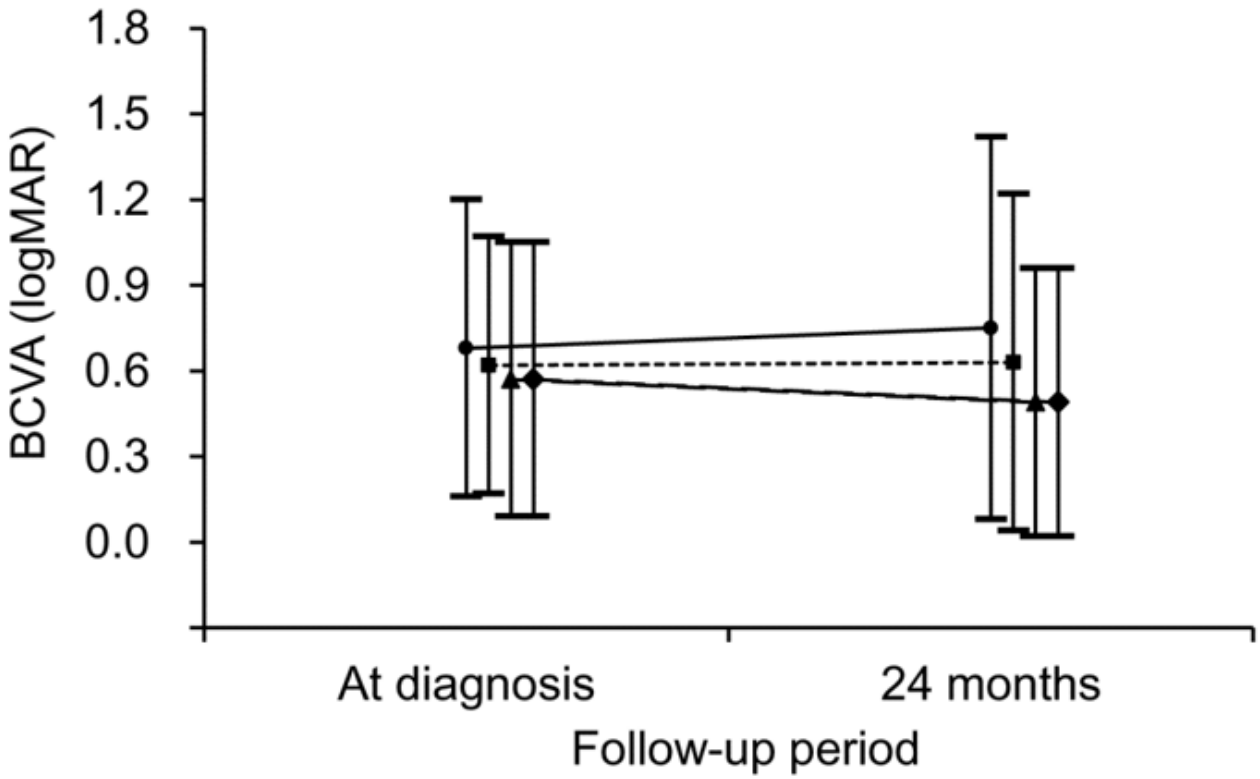

Figure 1

Time-dependent changes in best-corrected visual acuity (BCVA) in the 2013 (closed circle, solid line), 2015 (closed square, dotted line), 2017 (closed triangle, dashed line), and 2019 (closed diamond, dashed line) groups