

BMJ Open Healthcare resource use and costs of diabetic macular oedema for patients with anti-vascular endothelial growth factor versus a dexamethasone intravitreal implant in Korea: a population-based study

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ABSTRACT

Objectives To estimate the costs and healthcare resources of patients with diabetic macular oedema (DME) who received intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents or a dexamethasone intravitreal implant (DEX-implant) in Korea.

Design Retrospective cohort study.

Setting The Korean National Health Insurance claim data from 1 January 2015 to 30 June 2017 were retrieved from the Health Insurance Review and Assessment Service.

Participants Adult patients with DME who were diagnosed with diabetic retinopathy or DME and received ranibizumab, aflibercept or a DEX-implant in conjunction with intravitreal injection were included. Patients whose primary diagnoses were age-related macular degeneration or retinal vein occlusion were excluded.

Main outcome measures Healthcare resource utilisation and costs related to DME in the 12-month postindex period.

Results During the study period, 182 patients and 414 patients were identified in the anti-VEGF and DEX-implant groups, respectively, and there was no significant difference in the demographic characteristics between the two groups. The outpatient eye care-related medical costs were US\$3002.33 for the anti-VEGF group vs US\$2250.35 for the DEX-implant group ($p < 0.0001$). After adjusting the relevant covariates based on the generalised linear model, the estimated outpatient eye care-related medical costs were 33% higher in the anti-VEGF group than in the DEX-implant group ($p < 0.0001$, 95% CI 22% to 45%). The utilisation pattern of the two groups showed no significant difference except for the number of intravitreal injections, which was higher in the anti-VEGF group (2.69 ± 2.29) than in the DEX-implant group (2.09 ± 1.37 , $p < 0.001$).

Conclusion The average annual eye-related medical cost of the DEX-implant group was significantly lower than that of the anti-VEGF group during the study period, which was mainly due to decreased utilisation of eye care-related injections. Further long-term studies are needed.

Strengths and limitations of this study

- Our study is the first attempt to investigate the healthcare resource utilisation of anti-vascular endothelial growth factor (anti-VEGF) versus the dexamethasone intravitreal implant (DEX)-implant among patients with diabetic macular oedema (DME) using population-based data in Asia.
- This study explored the relative healthcare utilisation of patients with DME and demonstrated that healthcare cost in the DEX-implant group was relatively cheaper than that in the anti-VEGF group.
- Various statistical approaches were applied to examine the robustness of the analysis.
- Due to the short study duration and off-label use of bevacizumab, further long-term studies using medical chart reviews should be conducted.

INTRODUCTION

Diabetic macular oedema (DME) is a common complication for patients with diabetes and the main cause of blindness in the non-elderly.¹ Based on previous reports, 20% of patients with type I diabetes and 25% of patients with type II diabetes will suffer from DME;² the 25-year cumulative incidences of patients with DME and clinically significant DME for patients with diabetes are 29% and 17%, respectively, and the risk of DME increases as the duration of diabetes increases.³ The number of adult patients with diabetes is expected to reach approximately 628.6 million in 2045, which is a 50% increase from 424.9 million in 2017.⁴ According to the 2013–2016 Korea National Health and Nutritional Examination Survey (KNHANES), approximately 5 million Korean adults aged 30 years or older have diabetes, which

comprises more than 1/3 of the Korean population.⁵ DME could soon pose significant health concerns in Korea as well as around the world.

Blindness significantly reduces patients' quality of life and independence⁶ and is the third most serious health condition among the major complications of diabetes.⁷ Patients with DME reportedly have lower vision-related quality of life than do patients with diabetic retinopathy, patients with glaucoma and patients with cataracts.⁸

Additionally, patients with DME tend to have more comorbidities and consume more healthcare resources than do patients with diabetes without DME.^{9 10} The annual medical costs for patients with DME were approximately 30% higher than those for patients with diabetes without DME, and patients with DME were more than three times more likely to have ophthalmic visits after DME diagnosis (average 3.9 times) than were those without DME.¹¹ Gonder and colleagues reached a similar conclusion and suggested that DME poses a significant economic and health burden in Canada.⁶

Treatment options for DME include laser photocoagulation, intravitreal agents such as antivascular endothelial growth factor (anti-VEGF) and steroids.¹² Intravitreal injection is preferred over laser photocoagulation for the treatment of DME-associated visual impairment^{12 13} since patients with vision loss are less likely to experience significant improvements in best-corrected visual acuity after laser treatment, and improvement tended to slowly occur.^{14 15} Sustained-release corticosteroids have been developed to reduce the number of intraocular injections. The dexamethasone intravitreal implant (DEX-implant) is a sustained-release biodegradable implant indicated for the DME.¹⁶ Vascular endothelial growth factor (VEGF) is an important mediator of blood-retina barrier breakdown.¹⁷ Therefore, therapy that inhibits VEGF represents an effective therapeutic modality targeting the underlying pathogenesis of DME.¹⁴

Intravitreal injection of anti-VEGF agents is predominantly used for DME treatment, and two have been listed for DME by the Korean National Health Insurance (NHI): ranibizumab (Lucentis) since February 2015 and aflibercept (Eylea) since June 2015.¹⁸ Bevacizumab (Avastin), another anti-VEGF therapy, is used in Korea without regulatory approval (off-label use) and is not listed by the Korean NHI for DME.¹⁸ Sustained-release steroids made for intravitreal injection are another drug of choice for vision-impaired patients with DME, and the DEX-implant (Ozurdex), which falls into this category, has been listed in the Korean NHI since February 2016.¹⁸

Although both DEX-implant and anti-VEGF have shown similar efficacy in clinical trials,^{13 19} they have different pros and cons. DEX-implant can be administered less frequently (every 4–6 months),¹⁶ whereas anti-VEGF may be administered every 4–6 weeks.^{15 20 21} However, the DEX-implant is associated with an increased risk of cataracts or increased intraocular pressure.¹⁶ Thus, whether the DME-related healthcare resource utilisation of anti-VEGF users is lower or higher than that of DEX-implant

users is unclear. Given that DME causes a significant disease burden, it is important to evaluate the healthcare utilisation pattern of patients with DME between anti-VEGF users and DEX-implant users. However, few studies have examined the healthcare resource use of these two groups using a population-based database.

We sought to compare the direct healthcare costs and the healthcare utilisation patterns of patients with DME using anti-VEGF (ranibizumab and aflibercept) or the DEX-implant by employing the Korean NHI database. Specifically, we compared the demographic characteristics and medical costs of the patients with DME using anti-VEGF or the DEX-implant. Bevacizumab was not included since it was not listed by the Korean NHI for DME.

MATERIALS AND METHODS

Data source

We used the Korean NHI claim database, which covers approximately 97% of the Korean population of 48.4 million. The rest of the population is covered by the Medical Aid Program (MAP), a benefit programme for the underprivileged for which eligibility is determined based on patients' income level.²² The Health Insurance Review and Assessment Service (HIRA) provides access to the Korean NHI claim database with certain fees after the study protocol is evaluated. Access is allowed for a limited period for pre-specified individuals.²³

The Korean NHI is reimbursed mainly based on the fee-for-service system, and the NHI claim data are administrative data collected by the NHI for the purpose of reimbursements.²² The NHI claim data contain demographic information, diagnosis codes based on the International Classification of Diseases-10th Revision (ICD-10), procedures codes, claim dates, cost of the drug/procedure/visit, and pharmacy claim records. Pharmacy claim records include the number of prescriptions filled during the study period, whereas the prescription information covers the date and duration of the prescription, the prescribed drugs' international non-proprietary names, dosage, route of administration and the prescribers' identification number. The patient identification numbers were removed, but a unique number was assigned for each patient so that patient-level data could be generated.²² We obtained patient-level data from 1 January 2015 to 30 June 2017, which covers the total Korean population with specific diagnoses, procedures, and medication records during that period. The study was approved by the Ewha Womans University Institutional Review Board (IRB File No. 150–1).

Study population

We conducted a retrospective cohort study from 1 January 2015 to 30 June 2017, to estimate the anti-VEGF agent or DEX-implant user's medical usage pattern and burden of disease. Patients aged 18 and older who were diagnosed with diabetic retinopathy (Korean classification of disease-7th revision (KCD-7) code H360) or retinal

oedema (KCD-7 code H3580) based on their 5th diagnosis on the claim and received ranibizumab, aflibercept or DEX-implant in conjunction with intravitreal injection (Korean Current Procedural Terminology (CPT) code S5070.xx) in the index period (1 February 2016 to 30 June 2016) were included. Since we used the Korean NHI claim database and bevacizumab is not reimbursed for DME, we could not include bevacizumab. The index date or cohort entry date is the day that the patient with DME visited the ophthalmologic clinic during the index period and received the first study drug (ranibizumab, aflibercept or DEX-implant) with an intravitreal injection.

Patients with DME were classified as the anti-VEGF cohort and the DEX-implant cohort based on their medication utilisation pattern in the index period, and those patients who received the same medication in the postindex period and made at least three ophthalmic-outpatient visits during the follow-up period (1 year from the index date) were analysed for our analysis. Since patients with DME need to be monitored at least quarterly, we included patients who had at least three ophthalmic visits as the study populations. Medication claim records whose primary diagnoses were age-related macular degeneration (KCD-7 code H3530, H3531, and H3539) or retinal vein occlusion (KCD-7 code H348 and H349) were excluded for the analyses. We set the index period to reflect the Korean NHI listing date of the DEX-implant in Korea (1 February 2016).

Patients' baseline characteristics, such as age and gender, were measured at the index date. The Charlson comorbidity index (CCI), which measures a patient's comorbidity and is frequently used to adjust a patient's comorbidity, was measured in the preindex period, which is 1 year before the index date.²⁴ The provider's specialty and the types of medical institutions visited by patients with DME were also measured at baseline. The study design is shown in figure 1.

Outcomes

The primary outcome was the total annual medical cost per patient with DME that was reimbursed by the Korean NHI. Any healthcare utilisation that occurred for patients with DME during the 12 month postindex period was aggregated to estimate the total healthcare costs, and then this healthcare utilisation was categorised as outpatient/eye care-related utilisation based on the claim category (eg, outpatient) and provider's specialty (eg, ophthalmologist) on the claim. Namely, outpatient eye

care-related medical costs were estimated by summing all of the claims that occurred for the patient with DME in an outpatient setting by the ophthalmologist during the postindex period. The monetary value was estimated based on Korean won (KRW) with US\$1 translating into approximately 1100 KRW as of May 2018.

The secondary outcome was the number of visits and number of DME-related therapeutic and diagnostic procedures received per patient with DME during the postindex period. Optical coherence tomography (Korean CPT code EZ796), fluorescein angiography (FA) (Korean CPT code E6681 and E6682), fundus examination (Korean CPT code E6660), fundus photography (Korean CPT code E6670 and E6674), tonometry (Korean CPT code E6751 and E6752), slit-lamp biomicroscopy (Korean CPT code E6810) and intravitreal injection (Korean CPT code S5070.xx) that occurred during the postindex period were aggregated per patient with DME and compared between the two cohorts.

Statistical analysis

We used descriptive statistics to assess differences between patients who had anti-VEGF or the DEX-implant using χ^2 tests and Fisher's exact tests. If the cell sizes were less than 5, then we used Fisher's exact test. Because the medical costs and visit days were skewed, we specified a log link with gamma distribution.²⁵ We analysed the likelihood-ratio test for the generalised linear model (GLMs) for the variables related to costs and visit days. To estimate the unadjusted and adjusted effects of the two groups on the medical cost and visit days, we used GLMs.²⁶ For the adjusted effects, we adjusted the baseline characteristics such as age, gender, CCI and health plan type. These distributions of medical costs and visit days are non-parametric; thus, we evaluated healthcare utilisation using the Wilcoxon rank sum test. However, there was also a previous study regarding cost analysis that suggested a t-test in the guideline for comparing the average cost of the two groups;²⁷ thus, we presented both the t-test (for parametric) and Wilcoxon rank sum test (for non-parametric) for the costs and resource use to examine the robustness of the results. SAS software V.9.4 (SAS Institute, Cary, North Carolina, USA) was used for the analysis.

Patient and public involvement

Since we used the NHI claim database, individual patients were not involved in the study design. We could not disseminate the results of the research directly to study

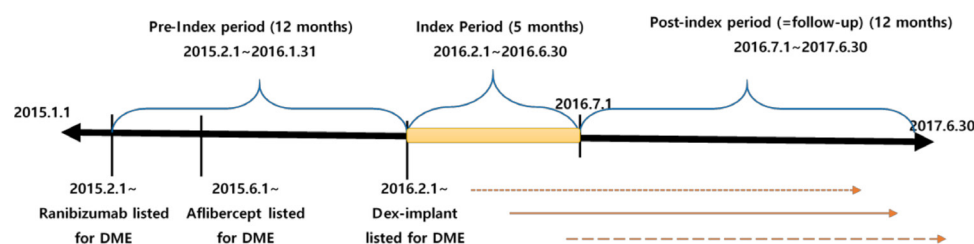


Figure 1 Study design. DME, diabetic macular oedema.

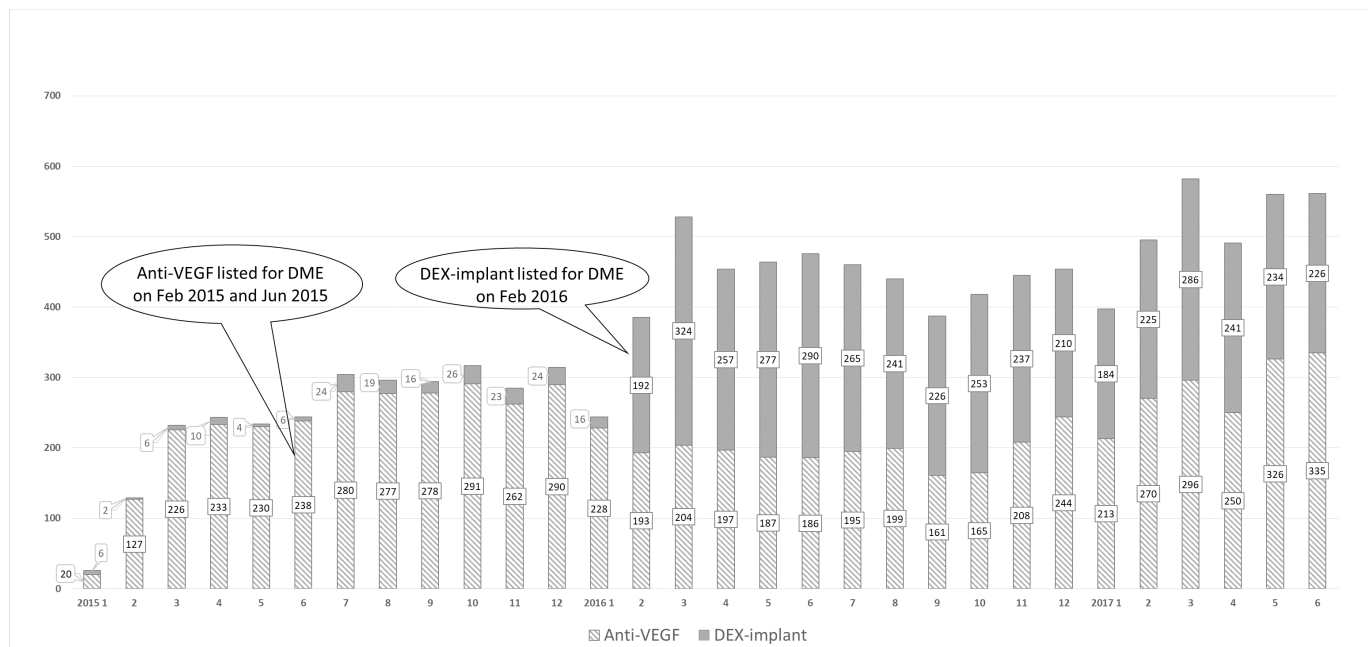


Figure 2 The number of patients with DME who received either anti-VEGF or a DEX-implant from 1.1.2015 to 30.6.2017. Anti-VEGF includes ranibizumab and aflibercept. Anti-VEGF, antivascular endothelial growth factor; DEX-implant, dexamethasone intravitreal implant; DME, diabetic macular oedema.

participants since patients' identifiable information was blocked by the HIRA.

RESULTS

During the study period, the number of monthly patients with DME who were treated with anti-VEGF or the DEX-implant increased from 26 patients in January 2015 to 561 patients in June 2017. With the DEX-implant listed since February 2016, the number of patients with DME using either anti-VEGF or the DEX-implant soared (figure 2).

For our cohort analysis, a total of 1486 patients with DME were treated with anti-VEGF agents (ranibizumab or aflibercept) or the DEX-implant during the index period. Of those 1486 patients with DME, only 596 were included for the analysis; 182 patients were treated with anti-VEGF, and 414 patients were treated with the DEX-implant alone during the follow-up period (890 of these patients were not included in the analysis). Of those 890 excluded patients, 727 did not receive any study medication during the follow-up period, although they had received the study medication during the index period at least once. We could not analyse these patients because there were no data for the follow-up period. A total of 109 of these patients switched the medication they received in the index period to the other group's medication during the follow-up period. Those patients were excluded because their switching pattern varied greatly, and the clinical rationale behind switching could not be found based on the claim database. Total 54 of these patients had fewer than three ophthalmic-outpatient visits (data not shown).

The demographic characteristics of the study population are shown in table 1. The average age for the anti-VEGF cohort and DEX-implant cohort was 58.6 vs 59.6, respectively, with no significant difference observed ($p=0.406$). Gender distribution and CCI distribution also showed no significant difference between the two groups. Although the CCI scores, which were measured 12 months prior to the index date, showed no significant difference ($p=0.083$), a higher percentage of anti-VEGF users had a lower score. In other words, 18.1% of the anti-VEGF and 10.6% of the DEX-implant fall into category 0, which indicates that a higher portion of anti-VEGF patients had fewer comorbidities (table 1). The proportion of anti-VEGF group patients (13.7%) insured under the MAP was significantly higher than that of DEX-implant group patients (5.1%, $p=0.0003$).

Table 2 shows the total medical cost, outpatient-medical cost, eye care-related medical cost, and outpatient-medical cost for ophthalmology for 12 months. Overall, the average total medical cost per person for the follow-up period was US\$6331.86 for the anti-VEGF group and US\$5708.54 for the DEX-implant group. The outpatient eye care-related medical cost was significantly different in the average medical cost (t-test, $p<0.0001$) and median medical cost (Wilcoxon rank sum test, $p=0.0012$), with a mean value of US\$3002.33 for the anti-VEGF group and US\$2250.35 for the DEX-implant group (table 2). After adjustment for age, gender, CCI and health plan type, the outpatient-medical cost and outpatient eye care-related medical cost were 20% and 33% higher in the anti-VEGF group than in the DEX-implant group, respectively ($p<0.0001$).

Table 1 Demographic characteristics of patients with DME who received either anti-VEGF agents or a DEX-implant during the study period

Variable	Anti-VEGF (n=182)	DEX-implant (n=414)	P value
Age, mean (SD), years	58.6 (12.6)	59.6 (10.8)	0.406
Age, n (%), years			0.409
18–39	10 (5.5)	22 (5.3)	
40–49	28 (15.4)	46 (11.1)	
50–59	54 (29.7)	127 (30.7)	
60–69	54 (29.7)	149 (36.0)	
70+	36 (19.8)	70 (16.9)	
Gender, n (%)			0.197
Male	101 (55.5)	206 (49.8)	
Female	81 (44.5)	208 (50.2)	
CCI, n (%)			0.083
0	33 (18.1)	44 (10.6)	
1	55 (30.2)	130 (31.4)	
2	43 (23.6)	103 (24.9)	
3	51 (28.0)	137 (33.1)	
Health plan type, n (%)*			0.0003
NHI	157 (86.3)	393 (94.9)	
MAP	25 (13.7)	21 (5.1)	

Age, gender and health plan type are analysed based on the index date. The CCI score is calculated for the 12 months from the start of the index date. P value estimated based on the χ^2 (categorical variables) and t-test (continuous variable).

*Korea has the NHI system for the general population and the MAP for the low-income people. The NHI system is for the entire population residing within the territory of Korea except for beneficiaries of medical aid.

anti-VEGF, anti-vascular endothelial growth factor; CCI, Charlson Comorbidity Index; DEX-implant, dexamethasone intravitreal implant; DME, diabetic macular oedema; MAP, Medical Aid Program; NHI, National Health Insurance.

Table 3 shows the healthcare visit days for the 12-month follow-up period between the two groups. The number of visits, such as the total number of visits, outpatient visits, and outpatient eye care-related visits, was not significantly different between the two groups.

Table 4 illustrates no significant difference in utilisation pattern between the two groups, except intravitreal injection, where both parametric ($p < 0.001$) and non-parametric ($p < 0.0044$) approaches achieved consistent results. Although significance was not achieved, the DEX-implant showed higher utilisation in tonometry based on the mean (12.08 vs 13.21) and median (11 vs 12).

DISCUSSION

We compared real-world healthcare utilisation of DME cohorts who were treated with anti-VEGF or the

DEX-implant and using data from the Korean NHI claim database. Although the number of patients in each cohort was rather limited, the average annual healthcare cost for patients with DME was approximately 6.9 million KRW (or US\$6331) for the anti-VEGF group and 6.2 million KRW (or US\$5708) for the DEX-implant group. Given that the annual cost per diabetes patient was 3.3 million KRW as of 2013,²⁸ the burden of DME is substantial.

However, there are few studies investigating the burden of patients with DME using population-based data, much less in Asia. In Canada, one prospective observational study on 145 patients investigated the DME cost by collecting the patients' medical charts and concluded that the average 6-month DME-related cost per patient was US\$2092, which translates into US\$4184 over 12 months.⁶ Given that our average annual eye care-related medical cost ranges from 3.4 million KRW (or US\$3161) for the anti-VEGF group and 3 million KRW (or US\$2751) for the DEX-implant group, our estimate is consistent with that of the Canadian study. Additionally, the Canadian study is based on a medical chart review, whereas our study is based on the administrative claim database; thus, our data could not incorporate non-reimbursed services and off-label use, such as bevacizumab. Bevacizumab is not indicated for DME and therefore is not listed by the Korean NHI; however, it is reportedly widely used due to its economic attractiveness. Thus, the two cohorts in our analyses might include patients with DME who were exposed to bevacizumab during the study period.

Further long-term studies are needed to investigate the relative utilisation of bevacizumab in two cohorts by examining medical charts. However, we assumed that the inclusion of bevacizumab would not significantly alter our findings since a previous study²⁹ based on a medical chart review showed that the utilisation pattern of bevacizumab would be similar to that of other anti-VEGF agents. Additionally, the rate of combination therapy (ie, bevacizumab + other anti-VEGF or bevacizumab + DEX-implant) would be low.

Additionally, our study was population-based; thus, our research does not suffer from selection bias, and the patient number is four times larger than that of the Canadian study.⁶ Few studies have examined the healthcare resource utilisation of anti-VEGF versus DEX-implant groups using population-based data. One US study compared bevacizumab versus the DEX-implant in 50 eyes and suggested that the number of injections in the DEX-implant group was significantly lower than that in the bevacizumab group.³⁰ Although our study medication does not include bevacizumab since it is not listed in the Korean NHI, one could argue that our result is consistent with the results of Shah and colleagues since bevacizumab is in a class of anti-VEGF agents. Given that the DEX-implant reportedly has a longer duration,³¹ our result is not surprising. The difference between two cohorts in the number of injections is not as dramatic as that in previous studies, which might be because aflibercept was included

Table 2 Annual healthcare cost for patients with DME who received either anti-VEGF agents or a DEX-implant

	Mean (US\$)		P value*	Median (US\$)		P value†	Unadjusted Cost ratio (95% CI)	Adjusted ‡ Cost ratio (95% CI)
	Anti-VEGF	DEX-implant		Anti-VEGF	DEX-implant			
Total medical cost§	6331.86	5708.54	0.2973	4232.36	3781.04	0.084	1.11 (0.97 to 1.27)	1.10 (0.97 to 1.26)
Outpatient-medical cost	4326.22	3747.87	0.0935	3461.67	2835.91	0.0008	1.15 (1.03 to 1.29)¶	1.20 (1.07 to 1.33)¶
Eye care-related medical cost	3161.42	2751.67	0.0222	2542.79	2365.60	0.1767	1.15 (1.04 to 1.26)¶	1.16 (1.05 to 1.27)¶
Outpatient eye care-related medical cost	3002.33	2250.35	<0.0001	2329.10	2069.86	0.0012	1.33 (1.22 to 1.46)**	1.33 (1.22 to 1.46)**

Anti-VEGF includes ranibizumab and aflibercept only. The total cost of medical care is the aggregated cost of all medical care used by the patient during a 1-year follow-up period. The cost was adjusted as of May 2018 in US dollars (US\$1 equals 1100 Korean won).

*Estimated p values based on the t-test.

†Estimated p values based on the Wilcoxon test.

‡Adjusted for baseline characteristics such as age, gender, CCI and health plan type.

§The cost of the DEX-implant group being referenced (1).

¶P<0.001.

**P<0.05.

anti-VEGF, anti-vascular endothelial growth factor; CCI, Charlson Comorbidity Index; DEX-implant, dexamethasone intravitreal implant; DME, diabetic macular oedema.

in our analysis, which reportedly has a longer duration than that of other anti-VEGF agents.³²

Our results suggested that the proportion of anti-VEGF group patients insured under the MAP was significantly higher than that of the DEX-implant group. Since the DEX-implant is more likely to be used by tertiary or teaching hospitals, whereas anti-VEGF is more likely to be used by the local or primary/secondary hospitals, and medical aid patients are more likely to visit local clinics rather than tertiary or teaching hospitals, our results can be interpreted based on the high correlation of the utilisation pattern of the medical aid patients and the types of drugs used by the medical institution³³

Although not significantly different, the tonometry utilisation pattern in the DEX-implant group was higher than that in the anti-VEGF group. This finding might be related to the ocular safety profile of the DEX-implant. 'Intraocular pressure increase' is an expected complication of corticosteroid treatment, such as the

DEX-implant.¹⁶ The difference in the tonometry utilisation pattern was predictable. Nonetheless, our analysis should be interpreted with caution, and further long-term study is needed to investigate the incidence of cataract and cataract-related healthcare utilisation in two treatment groups.

Additionally, since our study period was rather short (30 months), we had a short follow-up period and a limited preindex period, which prevented us from selecting newly diagnosed patients with DME for our analyses. Thus, the disease duration and clinical characteristics of our patients were diverse. Although no significant difference was found in terms of the CCI score in our analysis, further long-term study is needed to compare the two cohorts.

Healthcare cost data are usually skewed, and various measures, such as transformation or non-parametric methods, were considered. However, non-parametric methods also have their own drawbacks,²⁵ and using a

Table 3 Medical Institute visit days for patients with DME who received either anti-VEGF agents or a DEX-implant during the follow-up period

	Mean (days)		P value*	Median (days)		P value†	Unadjusted Visit ratio§ (95% CI)	Adjusted‡ Visit ratio (95% CI)
	Anti-VEGF	DEX-implant		Anti-VEGF	DEX-implant			
Total visits	55.59	51.45	0.3124	39.00	40.00	0.5176	1.08 (1.06 to 1.11)¶	1.07 (1.04 to 1.09)¶
Outpatient visits	45.26	44.20	0.7074	36.50	37.00	0.5787	1.02 (1.00 to 1.05)	1.05 (1.02 to 1.07)¶
Eye care-related visits	15.17	15.85	0.3449	14.00	14.00	0.4977	0.96 (0.92 to 1.00)	0.96 (0.92 to 1.00)
Outpatient eye care-related visits	14.97	15.14	0.8028	14.00	13.00	0.9359	0.99 (0.95 to 1.03)	0.99 (0.95 to 1.04)

Anti-VEGF includes ranibizumab and aflibercept. The total visits to medical care are the aggregated number of visits to all medical care used by the patient during a 1 year postindex period.

*Estimated p values based on the t-test.

†Estimated p values based on the Wilcoxon test.

‡Adjusted for baseline characteristics such as age, gender, CCI and health plan type.

§The reference values obtained from the DEX-implant as 1.

¶P<0.001

anti-VEGF, anti-vascular endothelial growth factor; DEX-implant, dexamethasone intravitreal implant; DME, diabetic macular oedema.

Table 4 Comparison of healthcare resource use related to ophthalmological diagnosis during the follow-up for patients with DME who received either anti-VEGF agents or a DEX-implant

	Mean (\pm SD)		P value	
	Anti-VEGF	DEX-implant	Parametric*	Non-parametric†
Optical coherence tomography	7.09 (\pm 3.38)	7.43 (\pm 3.15)	0.2383	0.3623
Fluorescein angiography	1.23 (\pm 0.56)	1.23 (\pm 0.48)	0.9852	0.6477
Fundus examination	9.25 (\pm 5.02)	9.73 (\pm 4.55)	0.2535	0.1126
Fundus photography	6.2 (\pm 3.80)	6.47 (\pm 3.86)	0.4571	0.4459
Tonometry	12.08 (\pm 6.09)	13.21 (\pm 7.09)	0.0502	0.1191
Slit-lamp biomicroscopy	12.4 (\pm 6.01)	13.15 (\pm 6.61)	0.1893	0.2375
Intravitreal injection	2.69 (\pm 2.29)	2.089 (\pm 1.37)	0.001	0.0044

Anti-VEGF includes ranibizumab and aflibercept.

*Estimated based on the t-test.

†Estimated based on the Wilcoxon test.

anti-VEGF, anti-vascular endothelial growth factor; DEX-implant, dexamethasone intravitreal implant; DME, diabetic macular oedema.

parametric approach to estimate the cost is endorsed.²⁷ Thus, both parametric and non-parametric approaches were used in our analysis. To compare the healthcare costs or visiting days between the two groups, we applied a parametric approach such as an independent two-sample t-test. However, because these variables are usually skewed, we also used non-parametric methods and gamma GLMs with a log link in our analysis.

Previous studies examined various clinically relevant outcomes, such as visual acuity or central subfield thickness,^{13 30} but clinical information is not available in the administrative claim database. Thus, we cannot conclude whether the reduced medical utilisation in the DEX-implant group could compromise the clinical outcome (such as aggravated visual acuity). According to Iglicki and colleagues,^{34 35} DEX-implant treatment is effective for improving vision in patients with DME and delaying progression to proliferative diabetic retinopathy during long-term follow-up (24 months), suggesting that the DEX-implant might be clinically beneficial as well as economically attractive.

Moreover, our study is the first population-based study in Asia, which describes the characteristics of patients with DME and their healthcare resource utilisation patterns.

Our study showed the relative frequency of intravitreal injection of two treatment groups using population-based, real-world data. The frequency of the injection can be associated with patients' treatment outcomes as well as the patients' attitude (convenience) towards the treatment.³⁶ Although the treatment regimen should be determined based on the clinical characteristics of each individual patient, providing the trend of the injection in two treatment groups could give clinicians a reference when they make decisions among many alternatives. Also, our findings could be attractive to policy makers who set priorities under budget constraint.

CONCLUSION

There was no significant difference in the demographic characteristics between the anti-VEGF and DEX-implant groups, and the DME-related healthcare resource utilisation of anti-VEGF users was higher than that of DEX-implant users. Specifically, the number of intravitreal injections and eye care-related medical costs for the DEX-implant group were lower than those of the anti-VEGF group. Further long-term studies are needed to investigate the impact of cataract, which is a side effect of the DEX-implant, and to enhance our findings on the relative utilisation of the two groups.

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