Executive Summary

Economic evaluation of intravitreal injection of anti-vascular endothelial growth factor in ocular diseases

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▢ Background

Because of population aging, the incidence of age-related macular degeneration (AMD) and diabetic macular edema (DME) is gradually rising; concomitantly, the use of anti-vascular endothelial growth factor (anti-VEGF) therapy, which is standard therapy for these diseases, is also increasing consistently. Spending for National Health Insurance (NHI) in Korea has grown continuously, reaching KRW 347.5 billion in 2015, and is expected to rise further. Because of the large budget impact, under NHI, the reimbursement of anti-VEGF therapy was limited to 14 times during a persons' lifetime until as recently as November 2017. Although AMD and DME are chronic diseases that require the therapy persistingly, the limited number of reimbursement resulted in the transference of a greater financial burden to the patient. For this reason, the reimbursement condition was lifted since December 1, 2017; instead, this limitation was revised such that the anti-VEGF therapy payments are no longer provided when corrected visual acuity is 0.1 or less even after each anti-VEGF drugs are administered five times. This new payment requirement is expected to change the patients' out of pocket and insurance spending in the future for the treatment of AMD and DME. This study aimed to examine related evidence for more effective and efficient policy implementation in the future.

▢ Objective

To compare and evaluate the efficacy and safety of anti-VEGF therapy on AMD or DME, two of the most burdensome retinal diseases, and analyze the budget impact of a newly established reimbursement requirement.

▢ Methods

First, we compared the efficacy and safety of the three anti-VEGF drugs (ranibizumab, aflibercept, and bevacizumab) that are used in Korea by using a systematic review, and evaluated the relative efficacy between these treatment alternatives.

Previous studies have focused on the differences in efficacy and safety of anti-VEGF drugs on patients with AMD or DME. In this study, we updated the existing systematic review in order to address the same key question. From among the current publications (21 for AMD, and nine for DME), we selected current papers that best fit the study's purpose, and included the randomized clinical trials (RCTs) that were reported since 2014. The papers were searched manually as well as by using three databases in overseas (Ovid-Medline, Ovid-Embase, and Cochrane Library). Two researchers reviewed the papers independently, and selected the ones for final inclusion in the study after reaching an agreement. A risk of bias assessment on the included papers was performed using Cochrane RoB; a meta-analysis was performed on efficacy and safety result variables, and a Bayesian network meta-analysis was conducted on the efficacy variable.

Second, we used National Health Insurance Service (NHIS)'s claims database (no.: NHIS-2017-1-210) to identify how anti-VEGF therapy was currently used on patients with AMD and DME. To obtain information of AMD and DME patients aged 18 or older including the number of patients, medical costs, and tendency of anti-VEGF therapy, we used NHI claims database based on the treatment start date from January 1, 2010 to December 31, 2016. To estimate medical cost related to retinal disease, we only analyzed the claims database in ophthalmology.

Third, we estimated changes in spending for NHI due to a newly introduced payment requirement for the next five years (2018 to 2022). In addition to the new payment requirement, the budget impact was analyzed on scenarios involving the introduction of biosimilars and the use of off-label drug, bevacizumab. We use the numbers of patients and therapies based on the NHI claims database and anti-VEGF cohort data. We also analyzed it dividedly payer's and patients' payments.

▢ Results

• A systematic review on the efficacy and safety of ranibizumab, bevacizumab, and aflibercept on AMD and DME revealed that there was no significant difference between the three drugs on AMD. With regards to DME, based on the best corrected visual acuity (BCVA) change as an efficacy variable, bevacizumab (SMD: -0.34; 95% CI: -0.53, -0.14) and ranibizumab (SMD: -0.20; 95% CI: -0.40, -0.01) had lower efficacy than aflibercept; no difference was found in the safety variables.

• The number of patients aged 18 or older who a received anti-VEGF intravitreal injection due to AMD or DME more than doubled in 2016 compared to 2009. As of 2016, Also, the number of ranibizumab and aflibercept injections used on those patients more than doubled in 2016, as compared to 2010. For the two diseases, each patient received therapy three times per year, and the existing limit of 14 payments was completely used up within four years.

• This study also performed an analysis on the budget impact of the new reimbursement criteria implemented in December 2017 on NHI. Spending for NHI was expected to increase greatly as the limit of 14 payments during a persons' lifetime was lifted, but instead, the spending was found to decrease a little. If additional policies including biosimilars to ranibizumab, or coverage for bevacizumab are introduced, spending for NHI is expected to be greatly reduced.

I. Efficacy and Safety Comparison between Anti-VEGF therapy

1. Age-related macular degeneration

After updating the existing systematic review, we finally chose 12 RCTs (19 papers), of which, 10 RCTs were focused on comparing ranibizumab and bevacizumab, and there were relatively fewer studies on the efficacy of aflibercept.

Based on efficacy indicators (change from baseline in best corrected visual acuity (BCVA), difference between intervention and comparator, change (gain or loss) in BCVA of 15 ETDRs letters), we performed a paired meta-analysis and found no significant difference in efficacy between ranibizumab, bevacizumab, and aflibercept. Since none of the RCTs compared bevacizumab and aflibercept, we performed a bayesian network meta-analysis. Our result indicated no significant difference in efficacy between ranibizumab, bevacizumab, and aflibercept.

A meta-analysis of paired comparison on safety result variables including mortality, arterial thromboembolic events, venous thromboembolic events, bacterial endophthalmitis, increased intraocular pressure, and retinal detachment, revealed no difference in risk between the drugs.

2. Diabetic macular degeneration

We selected six RCTs (nine papers) from the updated systematic review, for final inclusion in our study. Of the six RCTs, three were focused on comparing ranibizumab and bevacizumab, and there was only one trial for each drug; there was a lack of studies on comparative efficacy between different drugs. In addition, there were clinical trials than AMD.

Based on the efficacy indicators (change from baseline in BCVA, difference between intervention and comparator, change (gain or loss) in BCVA of 15 ETDRs letters), we performed a meta-analysis of paired comparison and found that in the change BCVA after anti-VEGF therapy, the efficacy of bevacizumab was significantly lower than that of aflibercept (SMD: -0.36; 95% CI: -0.55, -0.16). Moreover, the BCVA change indicator, which

compared visual acuity changes between the drugs before and after therapy, showed that ranibizumab (SMD: -0.20; 95% CI: -0.40, -0.01) and bevacizumab (SMD: -0.34; 95% CI: -0.53, -0.14) was less effective than aflibercept. No significant difference was found in the other indicators. A network meta-analysis revealed that in the BCVA after therapy, bevacizumab's efficacy was also lower than that of aflibercept (SMD: -1.53; 95% CI: -2.92, -0.19).

While this study performed a meta-analysis of paired comparison on safety result variables including mortality, arterial thromboembolic events, venous thromboembolic events, bacterial endophthalmitis, increased intraocular pressure, and retinal detachment, no difference in risk was found between medications.

II. Current Status of Anti-VEGF therapy in Korea

1. Age-related macular degeneration

The number of patients aged 18 or older who had received anti-VEGF intravitreal injection due to AMD was 236,158 in 2009, but increased to 537,528 in 2016, reflecting a 2.3-fold increase in 8 years. As of 2016, patients in their 70s accounted for the largest proportion (34.9%), followed by those in their 60s (28.0%). In 2016, the total medical cost for AMD patients was KRW 327.9 billion. Among those patients, the patients had anti-VEGF injection more than once was 9,961 in 2009, and increased to 35,762 in 2016, reflecting a 3.6 times increased.

This study examined the number of ranibizumab and aflibercept injections used on AMD by year. The results indicated that the number of injections increased from 27,792 in 2010 to 63,115 in 2016; each patient used the drug(s) three times per year, and the average treatment interval was 2.89 months. This increase in the number of injections used reflected not only the increase in the number of patients due to a prevalence increase, but also an increase in the number of injections per individual due to an eased reimbursement criteria. The previous reimbursed limit of 14 injections per

person was used up in 3.34 years (SD: 1.29 years) on average, and medical cost per patient was KRW 6.36 million per year.

2. Diabetic macular edema

The number of patients with DME, aged 18 or older was 397,956 in 2009, but increased to 721,310 in 2016, which was higher than that due to AMD. Unlike AMD, those in their 60s accounted for the largest share (31.3%) as of 2016, followed by those in their 70s (27.8%). In 2016, the number of DME patients was higher than that of AMD patients, but its associated total medical cost was KRW 251.3 billion, which was lower than that of AMD. Among DME patients, ones received anti-VEGF injection more than once appeared to be 4,283 in 2015 and 4,270 in 2016.

This study examined the number of ranibizumab and aflibercept injections due to prevalence of DME by year; even though it slightly increased from 3,787 in 2015 to 3,997 in 2016, anti-VEGF injections were used relatively less in DME, compared to usage in AMD. Each patient used the drug(s) three times annually, and the average injection interval was 2.28 months, which was slightly shorter than that of AMD. In overall, the percentage of patients using anti-VEGF was lower, resulting in the smaller number of injections in DME. The average medical expenditure was estimated to be KRW 3.80 million per year.

III. Budget Impact of the New Reimbursement Condition for Anti-VEGF injection

1. Age-related macular degeneration

If the previous reimbursement condition (14 injections per persons' lifetime) continued with the current use trend (Scenario 1), it is estimated to NHI budget impact KRW 440.3 billion for the next 5 years from 2018. Under the new reimbursement condition in December 2017 (Scenario 2), where a patient is not eligible for reimbursement when there is cicatrization or severe contraction, and NHI reimbursement are not provided when corrected

visual acuity is 0.1 or less after five times of each anti-VEGF injection, the NHI spending is estimated at around KRW 560.1 billion for the next five years. While it was expected that spending for NHI would increase greatly as the limit of 14 injections per lifetime was removed, the actual effect turned out to be relatively small. Since NHI spending is expected to increase due to the use of anti-VEGF injection among AMD patients, this study estimated that the budget impact when biosimilars are launched and reimbursed by NHI after 2020 (Scenario 3), and bevacizumab, which is not currently reimbursed by NHI, becomes eligible for NHI (Scenario 4), would be KRW 521 billion and KRW 419.7 billion, respectively. If spending for NHI continues to rise due to an increasing number of AMD patients caused by population aging, strategies to encourage a drop in drug price by introducing biosimilars and bevacizumab should be considered alternative strategies in the future with a concerns with sustainability of NHI.

2. Diabetic macular edema

For DME, the limit of 14 anti-VEGF injection during a patients' lifetime is still unchanged. This study estimated a budget impact on the NHI medical cost if the reimbursement condition for DME is revised as in AMD. Under the current reimbursement condition (14 injections per persons' lifetime; Scenario 1), it is estimated to NHI medical cost KRW 94.7 billion for the next five years from 2018. If the reimbursement condition was changed similar to that for AMD and based on visual acuity (Scenario 2), it is estimated to KRW 106.2 billion for the next 5 years, similar to that of Scenario 1. The difference between Scenarios 1 and 2 would be minimal because 14 injections would be used up during the 5-year period and subsequently, no payments would be provided after 5 years had lapsed. If biosimilars were launched and reimbursed for after 2020 (Scenario 3) and bevacizumab, which is not currently paid over the injection limit, were paid (Scenario 4), the budget impact is estimated at KRW 98.4 billion and KRW 79.5 billion, respectively. If NHI spending continues to rise due to an

increasing number of DME patients caused by increasing diabetes patients, strategies to encourage a drop in drug price by introducing biosimilars and bevacizumab should be considered policy alternatives in the future with a concerns with sustainability of NHI. Accordingly, it seems reasonable to revise the current limit of 14 injections to be more applicable to clinical practice.

▢ Conclusions

This study aimed to examine evidence for the efficacy and safety of an anti-VEGF intravitreal injection, which has become a major therapy for two ocular diseases, AMD and DME. More specifically, this study compared and evaluated the efficacy and safety of ranibizumab, aflibercept, and bevacizumab, which are anti-VEGF drugs used in Korea. As a result, no significant difference between the anti-VEGFs was found for the treatment of AMD, whereas, aflibercept was found slightly more effective in the treatment of DME than ranibizumab and bevacizumab. While there was some safety concern about bevacizumab, which is not currently reimbursed by NHI in Korea, no evidence was found to determine whether bevacizumab was less safe than ranibizumab and aflibercept at this point.

Using the NHI claims database given by NHIS, we examined the use of ranibizumab and aflibercept, which are covered by NHI, and found that the use of these two drugs in both diseases had consistently grown; since aflibercept was covered and paid in 2014, it tended to replace ranibizumab rapidly. Based on this finding, we analyzed the budget impact of a new reimbursement condition implemented in December 2017 on NHI While it was expected that spending for NHI would increase sharply as the limit of 14 injections per persons' lifetime was lifted, the results showed that the changed requirement reduced spending for NHI even though the payments based on visual acuity were not discontinued significantly in practice. If NHI's financial burden of anti-VEGF injections continues to increase due to an high incidence in the future, policy decisions will be required concerning

the use of biosimilars, bevacizumab and other treatment alternatives in view of the sustainability of NHI.

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Key words

age-related macular degeneration, diabetic macular edema, anti-vascular endothelial growth factor therapy, efficacy, safety, budget impact