Repeated intravitreal injections of antivascular endothelial growth factor in patients with neovascular age-related macular degeneration may increase the risk of ischemic optic neuropathy

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Research article

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Abstract

Background Previous case reports presented the occurrence of ischemic optic neuropathy (ION) following intravitreal injections of antivascular endothelial growth factor (anti-VEGF). However, no previous studies have investigated the impact of injection numbers on the risk of ION. The aim of our study was to investigate whether repeated intravitreal injections of anti-VEGF would increase the risk of subsequent ION in patients with neovascular age-related macular degeneration (AMD). Methods A population-based, retrospective cohort study using the Taiwan National Health Insurance Research Database was conducted from 2007 to 2013. Neovascular AMD patients receiving intravitreal injections of anti-VEGF during the period were enrolled in the study cohort. Enrollees were divided into three groups according to categorized levels of injection number (first level: < 10 times, second level: 10–15 times, third level: > 15 times). Kaplan-Meier curves were generated to compare the cumulative hazard of subsequent ION among the three groups. Cox regression analyzes were used to estimate crude and adjusted hazard ratios (HRs) for ION development with respect to different levels of injection numbers. Confounders included for adjustment were age, sex, and comorbidities (diabetes, hypertension, hyperlipidemia, ischemic heart disease, and glaucoma). Results In total, the study cohort had 77210 patients. Of these, 26520, 38010, and 12680 were in the first, second, and third level groups, respectively. The Kaplan-Meier method revealed that the cumulative hazards of ION were significantly higher in those who had a higher injection number. After adjusting for confounders, the adjusted HRs for ION in the second and third levels of injection number were 1.91 (95% confidence interval [CI], 1.32–2.76), and 2.20 (95% CI, 1.42–3.43), respectively, compared with the first level. Conclusions Among patients with neovascular AMD, those who receive a higher number of anti-VEGF injections are at a significantly higher risk of developing ION when compared with individuals who receive a lower number of injections.

Background

Neovascular age-related macular degeneration (AMD) is characterized by the proliferation of abnormal blood vessels (neovasculatures) in the choroid and can cause severe vision loss. Inhibition of vascular endothelial growth factor (VEGF) leads to marked decreases in neovascularization of both the choroid and retina [1-4]. Thus, intravitreal injection of anti-VEGF has been widely performed to treat neovascular AMD.

Ischemic optic neuropathy (ION), resulting from an insufficient blood supply, is the most common acute optic neuropathy in older patients [5, 6]. ION is classified as anterior or posterior ION according to the affected segment of the optic nerve. Both segments are further categorized into arteritic (related to vasculitis), and nonarteritic (not related to vasculitis). Of these, the nonarteritic anterior ION (NAION) is the most common type. Risk factors for NAION include a crowded optic disk, diabetes, hypertension, hyperlipidemia, and ischemic heart disease [7-11]. Diminished ocular blood perfusion due to elevated intraocular pressure (IOP) or glaucoma could also precipitate the occurrence of ION [12-17].
Although intravitreal injection of anti-VEGF is effective in treating neovascular AMD, it may have some possible complications such as endophthalmitis, intraocular inflammation, IOP elevation, and ocular hemorrhage [18]. Besides, one rare ocular adverse effect is ION [19-21]. The underlying pathogenesis of the association between anti-VEGF and the risk of subsequent ION is still not fully known. One potential mechanism may be the transient IOP elevation after intravitreal injection of anti-VEGF. If this is the case, then increasing the numbers of injections may increase the risk of developing ION. To the best of our knowledge, no previous studies have investigated the impact of injection numbers on the risk of ION. The lack of evidence-based studies results from the rare occurrence of ION. Besides, systemic diseases such as diabetes, hypertension, hyperlipidemia, ischemic heart disease, as well as glaucoma, may confound the association between anti-VEGF and ION, and thus had to be adjusted.

We conducted this study based on the Taiwan National Health Insurance Research Database (NHIRD) to elucidate the association between intravitreal injection of anti-VEGF and subsequent ION. Our hypothesis is that a higher number of intravitreal injections of anti-VEGF will increase the risk of subsequent ION among neovascular AMD patients. We used the whole population database and therefore had large numbers of patients as well as a high level of statistical power. The completeness of the database ensures that the diagnoses of each patient available, and the diagnoses were according to the generally accepted International Classification of Diagnoses, Ninth Revision, Clinical Modification (ICD-9-CM) Codes.

**Methods**

**Data source**

The NHIRD was derived from the Taiwan National Health Insurance Program, which covers more than 99% of Taiwan's 23 million residents. The NHIRD consists of diagnoses, medical prescriptions, surgical procedures, insurance registry, and is released for scientific research after personal identification numbers have been encrypted. This study was approved by the institutional review board of National Yang-Ming University Hospital (2015A018).

**Study subjects**

We conducted a retrospective cohort study from January 1, 2007, to December 31, 2013. First, we selected patients from the NHIRD who were diagnosed with neovascular AMD (ICD-9-CM code 362.52) during the study period, which required confirmation by fundoscopy, fluorescein angiography, and/or optical coherence tomography. Patients diagnosed with neovascular AMD before the end of 2006 were excluded to ensure that all enrolled patients had new-onset neovascular AMD. Among them, those who received intravitreal anti-VEGF injections for the treatment of neovascular AMD were included in the study cohort. According to the number of anti-VEGF injections, patients in the study cohort were further divided into three groups (first level: < 10 times, second level: 10–15 times, third level: > 15 times).
Outcome variable

Patients in the study cohort were followed to identify the onset of ION (ICD-9-CM codes 377.41). Those with ION before the injection of anti-VEGF were excluded to ensure that all events of ION were new-onset.

Demographic variables and comorbidities

Demographic variables such as age and sex were extracted from the database. Age was categorized into three levels: the first (< 60 years), the second (60–75 years), and the third (≥ 75 years) level. Risk factors of ION such as diabetes (ICD-9-CM Codes 250), hypertension (ICD-9-CM Codes 401–405), hyperlipidemia (ICD-9-CM Codes 272), ischemic heart disease (ICD-9-CM Codes 410–414), and glaucoma (ICD-9-CM Codes 365) may confound the relationship between anti-VEGF and ION. Therefore, these comorbidities were identified in the medical records and included as covariates in our analyses.

Statistical analysis

Characteristics of the study cohort were presented according to age, sex, and comorbidities (e.g., diabetes, hypertension, hyperlipidemia, ischemic heart disease, and glaucoma). Group differences (first level: < 10 times, second level: 10–15 times, third level: > 15 times) in these variables were analyzed by ANOVA tests (for continuous variables) and chi-square tests (for categorical variables). Then, the study cohort was followed until the occurrence of ION, dropout from the database, or the end of 2013, whichever came first. Survival analysis using the Kaplan-Meier method with the log-rank test was applied to describe and compare cumulative hazard curves of ION, according to different levels of injection number.

Subsequently, all these variables (age, sex, number of intravitreal anti-VEGF injection, and comorbidities) were included in the Cox regression analyzes. Unadjusted hazard ratios (HRs) for ION were computed according to each variable in univariate analyzes. Then, adjusted HRs for ION were derived from multivariate analyzes. Comorbidities were regarded as time-dependent variables. All statistical operations were performed using SAS statistical package, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Demographic and clinical characteristics of the study sample
In total, 77210 patients were enrolled in the study cohort. Of them, 26520 were in the first level group, 38010 were in the second level group, and 12680 were in the third level group. Table 1 presents their demographic and clinical characteristics. The mean age in the study cohort was 67.4 years. The male to female ratio was 1.7:1. The prevalence of comorbidities was 35.6% for diabetes, 64.6% for hypertension, 44.3% for hyperlipidemia, and 29.8% for ischemic heart disease. Besides, 16.5% of the study cohort had glaucoma. The mean number of injections among the study cohort was 12.0, with a standard deviation (SD) of 2.9. Almost 50% of the patients had injection numbers in the range of 10 to 15. Significantly differences were found across the three groups (first level: < 10 times, second level: 10–15 times, third level: > 15 times) in age, gender, and comorbidities. The follow-up period of the study cohort was 3.50 ± 1.86 (mean ± SD) years, and did not differ significantly among the three groups. Of 77210 patients, 180 (0.23%) had a subsequent occurrence of ION, including 40 (0.15%) in the first level, 100 (0.26%) in the second level, and 40 (0.32%) in the third level group.

Kaplan-Meier curves and log-rank test

Figure 1 illustrates the Kaplan-Meier curves of ION corresponding to each level of injection number. According to the log-rank test, the difference in cumulative hazards was significant ($p < 0.01$).

ION risk

Table 2 displays HRs for ION with regard to age, sex, injection number, and comorbidities. In the univariate Cox regression analysis, the second level (10–15 times) and the third level ($\geq 15$ times) of injection number yielded an unadjusted HR for ION of 1.75 (95% confidence interval [CI], 1.21–2.53) and 1.99 (95% CI, 1.28–3.08), respectively, compared with the first level (< 10 times) of injection number. Adjusted HRs obtained by comparing the second and third levels with the first level of injection number were 1.91 (95% CI, 1.32–2.76) and 2.20 (95% CI, 1.42–3.43), respectively. Diabetes significantly increased the risk for ION in both the univariate and multivariate analyzes. However, age, sex, hypertension, hyperlipidemia, and ischemic heart disease were not significant risk factors for ION in both the univariate and multivariate analyzes. Glaucoma increased the risk for ION in the univariate analysis, but the statistical significance was only marginal (unadjusted HR = 1.43; 95% CI, 1.01–2.03) and was not significant in the multivariate analysis (adjusted HR = 1.35; 95% CI, 0.95–1.92).

Discussion

This study is the first to reveal the increased risk of ION after repeated injections of anti-VEGF among neovascular AMD patients. In our population-based study, utilizing Taiwan’s NHIRD with a long (7-year) study period, we found that among patients with neovascular AMD, the risk of ION significantly increased in those who received more anti-VEGF injections, after adjusting for confounders.
AMD is a multifactorial disease, and advanced age is a main predisposing factor. In our study, the study cohort had a mean age of 67.4 years, and nearly one-third was older than 75 years. These results were compatible with a previous hospital-based study regarding anti-VEGF use among neovascular AMD in Taiwan [22]. It is noteworthy that the distribution of comorbidities in our study was higher than in those without AMD in another population-based study in Taiwan [23]. Besides, table 1 revealed significant differences in age, gender, and comorbidities by number of injections. Therefore, the group differences in these variables were adjusted in our following Cox regression analyses.

The Kaplan-Meier curves with the log-rank test (Fig. 1) and Cox regression analyzes (Table 2) in our study revealed that a higher number of injections were associated with a higher risk of subsequent ION. Very few case reports have described the onset of ION following intravitreal injection of anti-VEGF. Hosseini et al. reported a 72-year-old woman with NAION occurring one week after the second intravitreal injection of anti-VEGF under the indication of active subfoveal choroidal neovascularization [19]. In their 2009 case report, Ganssauge et al. presented a 51-year-old man with pseudoxanthoma elasticum who received an intravitreal injection for choroidal neovascularization secondary to angioid streaks. Two weeks later, NAION was observed [20]. Huang et al. described a case of a 38-year-old woman with diabetic retinopathy. Three weeks after intravitreal injection of anti-VEGF, anterior ION occurred [21]. Although the elevated IOP during intravitreal injection might have a compression effect on the optic nerve head, the three cases of ION did not have elevated IOP. It is possible that the IOP elevation was temporary and not detected or other pathogenesis such as anti-VEGF itself precipitated ION.

Previous studies have shown that VEGF plays a role in modulating both vascular tone and blood flow autoregulation [24]. Ameri et al. found that a sudden drop in effective VEGF concentration might be responsible for the closure of normal capillaries [25]. Therefore, anti-VEGF may diminish the blood perfusion to the optic nerve head and cause ION. Besides, VEGF has been reported to have both neurotrophic and neuroprotective effects [26]. In a diabetic rat model after intravitreal anti-VEGF injection, apoptosis in retinal ganglion cells increased [27]. Maybe the optic nerve head was also directly disturbed by anti-VEGF, and the influence was additive after repeated injections. Therefore, repeated injections of anti-VEGF lead to a higher risk of ION.

Our study has the strengths of a large sample size, an extended study period, a statistical analysis that adjusted for confounders, and validated diagnoses. In our health care system, the National Health Administration (NHA) frequently checks the cross-consistency of claims and chart data. The NHA also confirmed diagnoses that were approved by a standard protocol of examinations. Therefore, the diagnoses in our database have a high degree of accuracy.

The limitation of our study is that we cannot conclude a causal relationship between repeated anti-VEGF injection and ION. All analyzes were based on our database, and we derived a positive association between repeated anti-VEGF injection and ION. The underlying mechanism of the association is still not fully elucidated. Further basic research, animal models, and maybe large-scale prospective cohort studies are needed to unravel the pathogenesis.
At present, our study reminds ophthalmologists to check the optic nerve changes following the anti-VEGF injection among neovascular AMD patients, especially those who received a higher number of injections. The risk of ION should also be considered when deciding anti-VEGF injections as treatment for neovascular AMD.

**Abbreviations**

AMD: age-related macular degeneration; VEGF: vascular endothelial growth factor; ION: Ischemic optic neuropathy; NAION: nonarteritic anterior ION; IOP: intraocular pressure; NHIRD: National Health Insurance Research Database; ICD-9-CM Codes: International Classification of Diagnoses, Ninth Revision, Clinical Modification Codes; HRs: hazard ratios; CI: confidence interval; NHA: National Health Administration

**Declarations**

**Ethics approval**

This study was approved by the ethical committee of Yang-Ming University Hospital (2015A018).

**Consent for publication**

Not applicable.

**Availability of data and materials**

The dataset analyzed during the current study are available from the Collaboration Center of Health Information Application, Ministry of Health and Welfare, Taiwan: Stcarolwu@mohw.gov.tw, address: 4F., No.488, sec. 6. Zhongxiao E. RD., Nangang Dist., Taipei City 115, Taiwan.

**Completing interests**

The authors declare that they have no competing interests.

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Authors’ contributions

Conceptualization: YYC, PC, YFH, HJC, YCW, CCL, LYH, HHC; Formal analysis: YYC, PC, and HJC; Investigation: YYC, YCW, HHC, and CCL; Methodology: YYC, LYH, and HHC; Validation: YYC, PC, and YFH; Writing the original draft: YYC, and PC.

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**Tables**

**Table 1. Characteristics of the study cohort**
| Variable                  | Study cohort (n=77210) | First level (n=26520) | Second level (n=38010) | Third level (n=12680) | p-value |
|--------------------------|------------------------|-----------------------|------------------------|-----------------------|---------|
| Age, years               | 67.4±12.2              | 65.3±13.0             | 68.1±12.0              | 69.5±10.5             | <0.0001 |
| Age group, categorical   |                        |                       |                        |                       | <0.0001 |
| <60                      | 20020 (25.9)           | 8840 (33.3)           | 8940 (23.5)            | 2240 (17.7)           |         |
| 60–75                    | 32780 (42.5)           | 10400 (39.2)          | 16410 (43.2)           | 5970 (47.1)           |         |
| >75                      | 24410 (31.6)           | 7280 (27.5)           | 12660 (33.3)           | 4470 (35.2)           |         |
| Sex                      |                        |                       |                        |                       | <0.0001 |
| Male                     | 48570 (62.9)           | 15480 (58.4)          | 24490 (64.4)           | 8600 (67.8)           |         |
| Female                   | 28640 (37.1)           | 11040 (41.6)          | 13520 (35.6)           | 4080 (32.2)           |         |
| Number of injection, times | 12.0±2.9               | 8.7±3.4               | 12.3±1.7               | 18.1±4.2              | <0.0001 |
| Number of injection, categorical |                  |                       |                        |                       |         |
| First level (<10)        | 26520 (34.4)           | 26520                 | 0                      | 0                     |         |
| Second level (10-15)     | 38010 (49.2)           | 0                     | 38010                  | 0                     |         |
| Third level (≥15)        | 12680 (16.4)           | 0                     | 0                      | 12680                 |         |
| Diabetes                 |                        |                       |                        |                       | <0.0001 |
| Yes                      | 27490 (35.6)           | 10770 (40.6)          | 12510 (32.9)           | 4210 (33.2)           |         |
| No                       | 49720 (64.4)           | 15750 (59.4)          | 25500 (67.1)           | 8470 (66.8)           |         |
| Hypertension             |                        |                       |                        |                       | <0.0001 |
| Yes                      | 49900 (64.6)           | 16940 (63.9)          | 24420 (64.2)           | 8540 (67.3)           |         |
| No                       | 27310 (35.4)           | 9580 (36.1)           | 13590 (35.8)           | 4140 (32.7)           |         |
| Hyperlipidemia           |                        |                       |                        |                       | <0.0001 |
| Yes                      | 34200 (44.3)           | 11760 (44.3)          | 16480 (43.4)           | 5960 (47.0)           |         |
| No                       | 43010 (55.7)           | 14760 (55.7)          | 21530 (56.6)           | 6729 (53.0)           |         |
| Ischemic heart disease   |                        |                       |                        |                       | <0.0001 |
| Yes                      | 22990 (29.8)           | 7630 (28.8)           | 11350 (29.9)           | 4010 (31.6)           |         |
| No                       | 54220 (70.2)           | 18890 (71.2)          | 26660 (70.1)           | 8670 (68.4)           |         |
| Glaucoma                 |                        |                       |                        |                       | <0.0001 |
| Yes                      | 12730 (16.5)           | 4570 (17.2)           | 5890 (15.5)            | 2270 (17.9)           |         |
| No                       | 64480 (83.5)           | 21950 (82.8)          | 32120 (84.5)           | 10410 (82.1)          |         |
| Follow-up period, years  | 3.50±1.86              | 3.51±1.87             | 3.49±1.86              | 3.53±1.84             | 0.09    |
| Incident ION             | 180 (0.23)             | 40 (0.15)             | 100 (0.26)             | 40 (0.32)             | <0.01   |

ION ischemic optic neuropathy. Data are presented as mean±standard deviation or n (%).

**Table 2. Risk Factors for ION in the study cohort**
| Variables                          | Univariate analysis | Multivariate analysis |
|-----------------------------------|---------------------|-----------------------|
|                                   | Unadjusted HR (95% CI) | Adjusted HR (95% CI) |
| Age group, years                  | p-value             | p-value               |
| <60                               | Reference           | Reference             |
| 60–75                             | 1.02 (0.76–1.39)    | 1.01 (0.75–1.38)      |
| 75                                | 1.17 (0.86–1.61)    | 1.09 (0.76–1.58)      |
| Sex (male vs. female)             | 0.84 (0.65–1.09)    | 0.82 (0.63–1.07)      |
|                                    | 0.19                | 0.14                  |
| Number of injection               |                     |                       |
| First level (<10)                 | Reference           | Reference             |
| Second level (10-15)              | 1.75 (1.21–2.53)    | 1.91 (1.32–2.76)      |
|                                    | <0.01               | <0.001                |
| Third level (≥15)                 | 1.99 (1.28–3.08)    | 2.20 (1.42–3.43)      |
|                                    | <0.01               | <0.001                |
| Diabetes                          | 1.82 (1.36–2.44)    | 2.03 (1.46–2.81)      |
|                                    | <0.0001             | <0.0001               |
| Hypertension                      | 1.05 (0.83–1.35)    | 1.04 (0.85–1.30)      |
|                                    | 0.65                | 0.65                  |
| Hyperlipidemia                    | 1.27 (0.95–1.70)    | 1.04 (0.75–1.43)      |
|                                    | 0.11                | 0.83                  |
| Ischemic heart disease            | 1.16 (0.85–1.58)    | 1.20 (0.86–1.67)      |
|                                    | 0.35                | 0.29                  |
| Glaucoma                          | 1.43 (1.01–2.03)    | 1.35 (0.95–1.92)      |
|                                    | <0.05               | 0.09                  |

ION ischemic optic neuropathy; HR hazard ratio; CI confidence interval.

In the multivariable analysis, all other variables in the table were included for adjustment.

**Figures**
Kaplan-Meier curves for ischemic optic neuropathy among neovascular AMD patients who received intravitreal injections of anti-VEGF. Level 1 represents less than 10 times; level 2 represents 10 to 15 times, and level 3 represents more than 15 times.