Safety of intravitreal injections for the treatment of patients with diabetic retinopathy: a population-based study

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Conflict of interest: None. Funded by CIHR through the Drug Safety and Effectiveness Network

Background

Diabetic retinopathy is a leading cause of severe vision loss in adults worldwide. Anti-vascular endothelial growth factor (anti-VEGF) agents have been used to treat these patients, but real-world data on safety is lacking.

Objective

To determine the risk of adverse events related to intravitreal anti-VEGF (bevacizumab, ranibizumab, pegaptanib, and aflibercept) in patients with diabetic retinopathy.

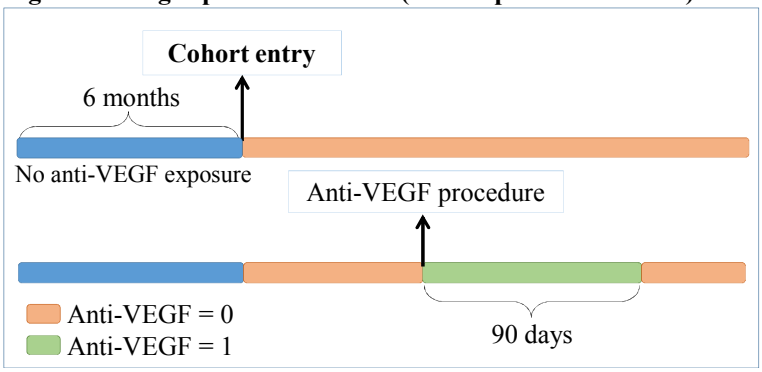
Methods

Study design: Survival analysis of diabetic retinopathy patients identified within Truven Health MarketScan® Research Databases (2011-2014). A patient could contribute to the data with more than one treatment episode.

Exposure: Time-dependent variable for current use of anti-VEGF. For users, the value was 0 before the first anti-VEGF and changed to 1 at the date of injection and onward for a maximum period of 90 days; after that, patients were not considered currently exposed. For the non-user, the value remains as 0 during the follow-up (Figure 1).

Follow-up: From cohort entry (date of diabetic retinopathy diagnosis) until the occurrence of the event of interest or the earliest of: date of death, loss of medical and/or pharmacy coverage, or end of study period (December 31, 2014).

Figure 1. Drug exposure definition (time-dependent variable).



Primary outcomes - ocular events: endophthalmitis, rhegmatogenous retinal detachment, retinal tear, uveitis, and vitreous hemorrhage.

Secondary outcomes - systemic events: cerebrovascular accident, myocardial infarction, deep vein thrombosis, and pulmonary embolism.

Statistical analysis: Cox regression models adjusted for baseline age, sex, place of residence, socioeconomic status, co-morbidities, cataract surgery, drugs (antihypertensive agents, statins, clopidogrel, warfarin, Aggrenox®, and low-molecular-weight heparin), and a time varying indicator of previous use of anti-VEGF during follow-up.

Results

- 204,314 individuals were included (Table 1); 17,885 (8.8%) underwent at least one anti-VEGF injection during the follow-up, receiving a total of 77,426 injections.
- Median follow-up time was 2.2 years (interquartile range: 0.9; 3.3).
- Current use of anti-VEGF was associated with higher rates of both ocular and systemic events (Table 2).
- Multivariate hazard ratios for ocular and systemic events were higher for anti-VEGF use versus non-use (Table 3).

Table 1. Selected baseline characteristics of patients with diabetic retinopathy included in the cohort (N=204,314).

Characteristics	Overall cohort
Female sex, n (%)	96,818 (47.4)
Age at cohort entry, median (interquartile range)	61 (54-70)
Co-morbidities and procedures, n (%)	
Hypertension	142,730 (68.9)
Diabetes with chronic complications	127,513 (62.4)
Dyslipidemia	122,113 (59.8)
Glaucoma	33,310 (16.3)
Cerebrovascular disease	23,596 (11.6)
Cataract surgery	51,200 (25.1)
Drug use before cohort entry, n (%)	
Statins	126,225 (61.8)
Angiotensin-converting-enzyme inhibitors	88,480 (43.3)
Angiotensin receptor blockers	51,908 (25.4)
Clopidogrel	21,748 (10.6)

Table 2. Crude incidence and 95% confidence interval (CI) for primary and secondary outcomes.

Drug exposure	Events	Total person-years	Rate (per 100 p-y)	95% CI
Ocular events				
Non-use	19,617	423,101	4.6	4.6; 4.7
Anti-VEGF	1,528	10,237	14.9	14.2; 15.7
Systemic events				
Non-use	7,791	448,544	1.7	1.7; 1.8
Anti-VEGF	448	13,087	3.4	3.1; 3.8

Table 3. Adjusted hazard ratios (HR) for anti-VEGF use.

Outcomes	Adjusted HR	95% CI
Ocular events	2.97	2.81; 3.14
Systemic events	1.81	1.64; 2.00

Conclusions

Use of intravitreal anti-VEGF agents was associated with increased risk of ocular complications and systemic events. Some of the effect may be due to residual confounding. Future analysis will assess the risk of individual anti-VEGF agents.