Safety of anti-vascular endothelial growth factor (anti-VEGF) intravitreal injections for the treatment of patients with age-related macular degeneration (AMD)

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Background

AMD is the leading cause of blindness among Americans over 40 years of age. The use of anti-VEGF agents has dramatically changed the management of neovascular AMD, but there is a paucity of real-world safety data.

Objective

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

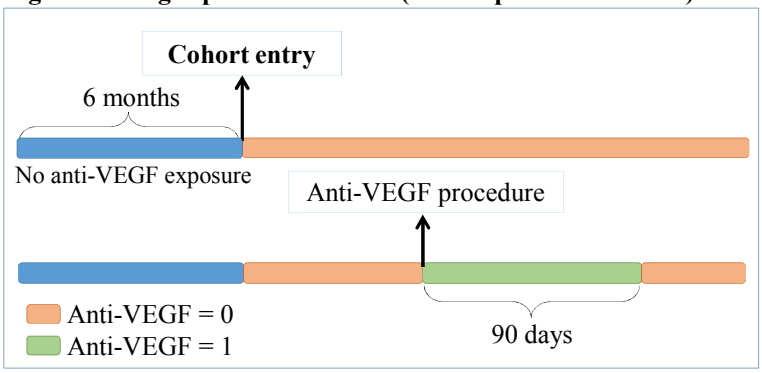
Methods

Study design: Survival analysis of neovascular AMD 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 neovascular AMD 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

- 104,941 individuals were included (Table 1); 18,977 (18.1%) underwent at least one anti-VEGF injection during the follow-up, receiving a total of 117,909 injections.
- Median follow-up time was 2.01 years (interquartile range: 0.96-3.00).
- 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 neovascular AMD patients included in the cohort (N= 104,941).

Characteristics	Overall cohort
Female sex, n (%)	64,505 (61.46)
Age at cohort entry, median (interquartile range)	79 (70-86)
Co-morbidities and procedures, n (%)	
Hypertension	69,185 (65.92)
Diabetes with chronic complications	7,616 (7.26)
Dyslipidemia	51,617 (49.18)
Cerebrovascular disease	16,199 (15.44)
Glaucoma	25,690 (24.48)
Cataract surgery	44,848 (42.73)
Drug use before cohort entry, n (%)	
Statins	49,841 (47.49)
Angiotensin-converting-enzyme inhibitors	27,008 (25.74)
Angiotensin receptor blockers	20,275 (19.32)
Clopidogrel	8,966 (8.54)

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	3,350	191,525	1.8	1.7; 1.8
Anti-VEGF	609	16,675	3.4	3.4; 4.0
Systemic events				
Non-use	3,338	192,947	1.7	1.7; 1.8
Anti-VEGF	401	17,032	2.4	2.1; 2.6

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

Outcomes	Adjusted HR	95% CI
Ocular events	2.24	2.05; 2.46
Systemic events	1.29	1.16; 1.44

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.