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ORIGINAL ARTICLE

Glaucoma progression in patients receiving intravitreal anti-VEGF treatment for neovascular age-related macular degeneration

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Abstract

Purpose: The purpose of this study was to investigate how often glaucoma and neovascular age-related macular degeneration (nAMD) occur in the same patient and to evaluate whether glaucoma progression is faster in eyes treated with intravitreal anti-VEGF medications for nAMD.

Methods: This single-centre retrospective real-world data (RWD) consists of medical records of 6314 glaucoma and 2166 nAMD patients treated in 2008–2017 in Tays Eye Centre, Finland. To study glaucoma progression, changes in visual fields (mean deviation [MD], dB/year), IOP (mmHg/year) and fundus photographs (progression, yes/no) were compared in glaucoma eyes with and without anti-VEGF treatment for nAMD and ≥1 year follow-up.

Results: During the 10-year period, 147 patients with glaucoma received intravitreal anti-VEGF treatment for nAMD corresponding to 2% of glaucoma and 7% of nAMD patients. The mean change in MD was −0.70 dB/year (SD 1.8) vs. −0.27 dB/year (SD 1.7) ($p = 0.027$) in glaucoma eyes with ($n = 37$) and without ($n = 4304$) anti-VEGF injections, respectively. In patients with bilateral glaucoma and unilateral nAMD treated with anti-VEGF injections ($n = 20$), MD declined at −0.62 dB/year (SD 1.9) vs 0.33 dB/year (SD 1.5) ($p = 0.654$), and glaucoma progression was detected in 14/20 vs 10/20 ($p = 0.219$) fundus photographs in eyes with anti-VEGF treatment compared with their untreated fellow eyes.

Conclusion: nAMD and glaucoma were found co-existing in the same eye at rates that were similar to the age-corrected prevalence of the two diseases in the general population. Our results suggest that intravitreal anti-VEGF treatment for nAMD may accelerate glaucoma progression.

KEYWORDS
AMD, anti-VEGF injections, glaucoma progression, real-world data

1 | INTRODUCTION

Age-related macular degeneration and glaucoma are the most common causes for permanent visual impairment in developed countries, including Finland (Resnikoff et al., 2004; Tuulonen et al., 2021). Glaucoma may be more common among patients with neovascular age-related macular degeneration (nAMD) than without nAMD (Hu et al., 2017). Intravitreal injections with anti-vascular endothelial growth factors (anti-VEGF) represent the mainstay therapy of nAMD (Kataja et al., 2018; Khanani et al., 2020). Although studies on glaucoma progression during anti-VEGF treatment for nAMD give mixed results, repeated anti-VEGF injections have been associated with an increased risk of glaucoma and ocular hypertension (Wingard et al., 2019). Anti-VEGF treatment has also been associated with an increased risk for glaucoma surgery (Du et al., 2019; Eadie et al., 2017).

According to a meta-analysis by de Vries et al. (2020) intraocular pressure (IOP) typically spikes after an anti-VEGF injection and then decreases rapidly over the next hour, dropping below the patient's baseline about a day later and returning to baseline after about a week (de Vries et al., 2020). A meta-analysis by Nanji et al. (2022) was not able to show any clear differences in IOP in 12–24 months of follow-up comparing eyes with and without

anti-VEGF. Nonetheless, a subset of patients may experience a clinically significant sustained IOP elevation following anti-VEGF treatment (Atchison et al., 2018).

Visual field (VF) progression may be faster in eyes with both glaucoma and nAMD requiring anti-VEGF treatment, but it is difficult to assess because the macular disease may also worsen the central visual field (Saleh et al., 2017). Du et al. (2019) reported a significant difference in VF progression rates comparing 28 eyes with anti-VEGF treatment (−1.07 dB/year) and without it (−0.01 dB/year).

Thinning of retinal nerve fibre layer (RNFL) and retinal ganglion cell layer may be faster in some eyes treated with anti-VEGF intravitreal injections compared with eyes without intravitreal injections (Abdolrahimzadeh et al., 2019; Beck et al., 2016; de Vries et al., 2020; Du et al., 2019; Shin et al., 2016). However, this finding was not confirmed by Rimayanti et al. (2014). We did not find any published studies in glaucoma patients with anti-VEGF intravitreal injections in which glaucoma progression was evaluated by fundus photographs.

The purpose of this study was to evaluate how often glaucoma and nAMD requiring anti-VEGF treatment occur in the same patients. The second objective was to evaluate whether glaucoma progression is more common or faster in glaucoma eyes with intravitreal anti-VEGF injections compared with glaucoma eyes without intravitreal injections.

2 | MATERIALS AND METHODS

This study is a sub-analysis of real-world data (RWD) collected for the 'Big 4' eye diseases which are AMD, glaucoma, diabetic retinopathy and cataract, containing overall 195 300 interventions in 2008–2020 in Tays Eye Centre, Tampere University Hospital, Finland (Tuulonen et al., 2021). For this single-center retrospective analysis, we included RWD collected manually from electronic medical records of all patients with 1) an ICD-10 code for nAMD (H35.31) and ≥1 CKD05-code for an intravitreal injection, and 2) patients with an ICD-10 code for glaucoma (H40.1, H40.2, H40.3, H40.4, H40.5, H40.6, H40.8, H40.9) and ≥1 visit in Tays Eye Centre, between 1 January 2008 and 31 December 2017. Patients with nAMD receiving laser photocoagulation, photodynamic therapy or intravitreal steroids were excluded from this analysis.

The following parameters were analysed: proportion of glaucoma patients and eyes receiving anti-VEGF intravitreal injections for nAMD, proportion nAMD patients receiving anti-VEGF treatment with concomitant glaucoma, age at the beginning of the follow-up, gender, type of glaucoma, total number of anti-VEGF injections, IOP, follow-up time and visual field mean deviation (MD) and change in MD. Visual fields of glaucoma patients were followed by 24–2 SITA program (Humphrey Field Analyser, Carl Zeiss Meditec, Dublin, CA, USA). Optic nerve head (ONH) and retinal nerve fibre layer (RNFL) were photographed using Canon CX-1 retinal camera (Canon, Tokyo, Japan) using a monochromatic blue interference filter (495 nm) for RNFL imaging.

To evaluate glaucoma progression, eyes with ≥1 year glaucoma follow-up were included in the analysis. For the analysis of change in IOP and MD in glaucoma eyes with anti-VEGF injections, eyes with IOP and MD measurement ≤1 year before and at least once ≥1 year after the first anti-VEGF injections were included. Mean change in IOP from baseline (the last IOP measurement before the first anti-VEGF injection) to the last IOP measurement at least 1 year after the first injection, and mean time between these IOP measurements were calculated. Due to the variability in follow-up periods, changes in IOP and MD were assessed per year (mmHg/year and dB/year) as the difference between the first and last measurements divided by the follow-up time. Fundus photographs taken ≤1 year before and at least once ≥1 year after the first anti-VEGF injections were evaluated for patients with bilateral glaucoma and unilateral nAMD receiving anti-VEGF treatment. Two glaucoma specialists (AT, SL) compared the baseline and the latest follow-up fundus photographs independently for any glaucomatous changes. Glaucomatous progression was labelled as 'yes' or 'no'. In case of disagreement, the specialists discussed to reach a consensus.

Injection Group 1 included eyes with both glaucoma and nAMD requiring anti-VEGF injections. When both eyes of a patient were eligible, one eye was randomly chosen for analysis. Noninjection Control Group 1 included all glaucoma eyes with ≥2 year IOP and MD follow-up during 2008–2017 and without anti-VEGF injections for nAMD. One eye per patient was chosen randomly for analysis (Table 1).

The Injection Subgroup 2 included patients from Injection Group 1 who had bilateral glaucoma and unilateral anti-VEGF treatment. Their untreated fellow eyes formed Noninjection Control Subgroup 2 (Table 2).

Statistical analyses were performed by a statistician (MH) using Statistical Package for Social Sciences (IBM SPSS Statistics 27, 2020). Mann–Whitney *U* test and Wilcoxon signed rank test were used to determine changes in MD and IOP between groups. McNemar's test was used to determine the difference in progression in the fundus photographs between groups. A p-value <0.05 was considered significant.

3 | RESULTS

During 2008–2017 in Tays Eye Centre, altogether 2750 eyes of 2156 patients (mean age 78, ± 8 years) with nAMD were treated with anti-VEGF therapy and 11 581 eyes of 6314 patients (mean age 69, ± 13 years) were followed up for glaucoma (Figure 1). Among them, 185 eyes of 147 patients had glaucoma and concomitant nAMD treated with anti-VEGF injections. Thus, 2% of glaucoma patients and eyes received anti-VEGF treatment for nAMD and 7% of nAMD patients had concomitant glaucoma.

Injection Group 1 included 37 eyes of 37 patients with glaucoma and concomitant nAMD (Figure 1). These eyes received a mean of 8 ± 6 anti-VEGF injections during 2008–2017 (Table 1). 30 eyes of 37 patients (82%) in Injection Group 1 received bevacizumab monotherapy while 7 eyes of 37 patients (18%) received both

TABLE 1 Data of Injection Group 1 and Noninjection Control Group 1 described in Figure 1.

	Injection Group 1	Noninjection Control Group 1
	37 eyes of 37 glaucoma patients with anti-VEGF injections	**4304 eyes of 4304 glaucoma patients without anti-VEGF injections[a]**
Mean age (SD)[b]	75 (7) years	68 (12)
Female gender	78%	63%
Mean duration of VF follow-up (SD)[b]	30 (18) months	50 (24) months
Mean duration of IOP follow-up (SD)[b]	36 (18) months	58 (26) months
Mean number of injections (SD)	8 (6)	NA
Mean IOP change per year (SD)[c]	−0.14 (2.23) mmHg	−0.89 (2.57) mmHg
Mean MD change per year (SD)[d]	−0.70 (1.81) dB	−0.27 (1.74) dB
Proportion of open angle glaucoma	46%	49%
Proportion of normal tension glaucoma	24%	19%
Proportion of exfoliative glaucoma	14%	14%
Proportion of other/not specified glaucoma	16%	18%

[a]IOP analysis in 4079 glaucoma patients.
[b]$p < 0.001$.
[c]Difference not statistically significant.
[d]$p = 0.027$ (Mann–Whitney U test).

TABLE 2 Data of Injection Subgroup 2 and Noninjection Control Subgroup 2.

	Injection Subgroup 2	Noninjection Control Subgroup 2
	20 glaucoma eyes with anti-VEGF injections	**20 glaucoma fellow eyes without anti-VEGF injections**
Mean age (SD)	74 (5) years	
Female gender	80%	
Mean follow-up time (SD)	28 (14) months	
Mean number of injections (SD)	7 (6)	NA
Mean IOP change per year (SD)[a]	+0.23 (2.78) mmHg	−0.35 (2.85) mmHg
Mean MD change per year (SD)[a]	−0.62 (1.93) dB	−0.33 (1.48) dB
Proportion of open angle glaucoma	50%	55%
Proportion of normal tension glaucoma	35%	30%
Proportion of exfoliative glaucoma	10%	10%
Proportion of other/not specified	5%	5%
Progression in fundus photographs[a]	70%	50%

[a]Difference is not statistically significant.

bevacizumab and aflibercept during the follow-up. Table 1 shows the demographics and clinical characteristics of Injection Group 1 and the Noninjection Control Group 1.

When comparing the Injection Group 1 to the Noninjection Control Group 1, the mean rate of VF progression was larger among the eyes receiving anti-VEGF treatment for nAMD (−0.70 ± 1.81 vs. −0.27 ± 1.74 dB/year, $p = 0.027$, Mann Whitney test). The mean VF follow-up for Injection Group 1 was 30 months. The mean IOP decreased in both Injection Group 1 and the Noninjection Control Group 1 during the follow-up (Table 1). The mean IOP changes in the injected cases compared with the noninjected controls were − 0.14 ± 2.23 vs −0.89 ± 2.57 mmHg/year ($p = 0.093$) (Table 1).

Injection Subgroup 2 included 20 eyes with glaucoma and concomitant nAMD with unilateral anti-VEGF treatment. Their fellow eyes with glaucoma and without anti-VEGF treatment for nAMD formed the Noninjection Control Subgroup 2 (Table 2). The MD changes in Injection Subgroup 2 compared with their controls were − 0.62 ± 1.93 vs −0.33 ± 1.48 dB/year ($p = 0.654$), respectively. Progression was observed in fundus photographs in 14/20 vs 10/20 ($p = 0.219$) eyes with and without anti-VEGF injections, respectively. Changes in IOP without anti-VEGF treatment compared with the fellow eyes receiving anti-VEGF treatment for nAMD were − 0.35 ± 2.85 vs +0.23 ± 2.78 mmHg/year ($p = 0.337$) (Table 2).

4 | DISCUSSION

Our study reveals that nAMD requiring anti-VEGF treatment occurred in combination with glaucoma at about the same rate as might be expected in the general population.

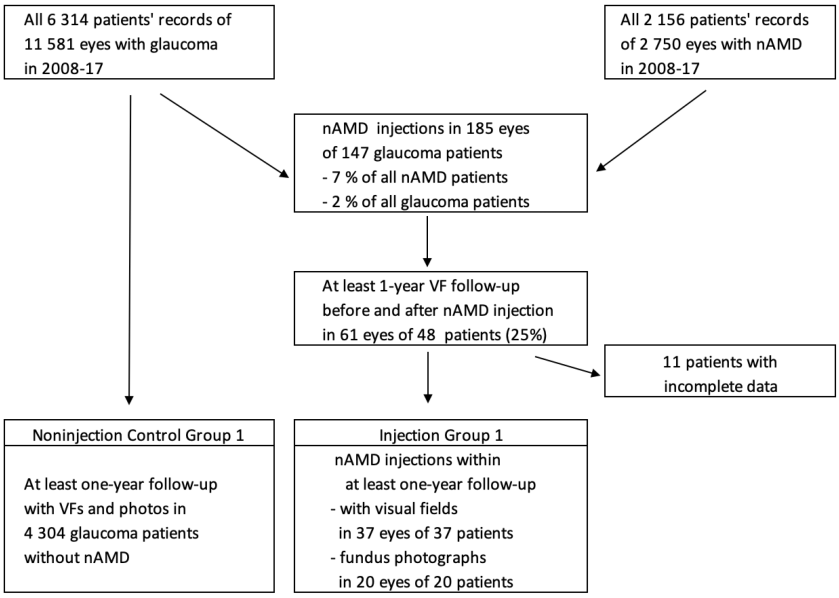

FIGURE 1 Flowchart of the patient material.

Despite the large real-world patient population with 6314 glaucoma patients and 2156 nAMD patients and a 10 years follow-up, only 147 patients had received treatment for both eye diseases. Considering that both glaucoma and nAMD requiring anti-VEGF treatment affect elderly patients who are under continuous surveillance, a larger overlap of these two diseases could be anticipated. To our knowledge, this is the first real-world data set with 10 years follow-up to report such occurrences.

Although earlier studies suggest an increased risk of glaucoma in nAMD (Hu et al., 2017; Wingard et al., 2019), the prevalence of glaucoma among nAMD patients treated with anti-VEGF did not differ from the general population in our study. The number of patients receiving medical therapy for glaucoma in Finland has been recently reported to be 7%–8% among 75–79 year olds (Vaajanen et al., 2021). That is, similar to our study in which 7% of patients with anti-VEGF-treatment for nAMD were treated for glaucoma.

The prevalence of nAMD increases with advancing age from 1% in 70–74 year olds, to 2% in 75–79 year olds and to 3%–6% in 80–84 year olds (Creuzot-Garcher et al., 2022; Sedeh et al., 2017). Among our glaucoma patients, the cumulative rate of nAMD with anti-VEGF treatment was 2% with the mean age of 74–75 years (Figure 1).

We found a statistically significant faster rate of VF progression among 37 glaucomatous eyes with anti-VEGF treatment for nAMD compared with a control group of 4304 eyes with glaucoma and without anti-VEGF for nAMD (Table 1). Also, in the study by Du et al. (2019), visual field deterioration was greater in eyes receiving anti-VEGF treatment. In their study, MD declined faster with anti-VEGF treatment (−1.07 dB/ year) than without (−0.01 dB /year). When interpreting these results, it is important to recognize that central visual field defects may also worsen following macular scarring and not just glaucoma progression.

There also was a trend towards a higher rate of VF progression among 20 eyes with anti-VEGF treatment for nAMD compared with their 20 untreated fellow eyes (Table 2). Like in most studies dealing with the long-term effects of intravitreal anti-VEGF treatment (Levin et al., 2021), the sample size for Injection Group 2 was too small to detect difference in MD progression rates between the cases and controls to reach statistical significance.

Glaucoma progression detected in fundus photographs may have been somewhat more prevalent in nAMD eyes undergoing anti-VEGF therapy than their untreated fellow eyes (Table 20). However, either the sample size and/or differences in progression rates may have been too small for the finding to reach statistical significance. We were unable to find any previously published studies that used ONH or RNFL photographs to examine glaucoma progression in nAMD. Previously, however, a similar trend for disease progression has been reported in OCT follow-up studies (Beck et al., 2016; Shin et al., 2016).

In the Injection Subgroup 2, there seemed to be a trend for a less favourable long-term IOP level with anti-VEGF treatment (+0.23 mmHg/year) than without (−0.35 mmHg/year) (Table 2), similar to Injection Group 1 with a smaller IOP change after anti-VEGF treatment (−0.14 mmHg/year) than in the untreated controls (−0.89 mmHg /year) (Table 1). The long-term impact of anti-VEGF injections on IOP remains unresolved in our study and other studies (Hoguet et al., 2019). Because our routine care process does not include routine short-term IOP measurements after anti-VEGF injections, these data are not available.

Our study confirms several challenges that have been encountered in previous studies as well (Levin et al., 2021). Visual field data were available in only 20% of patients with glaucoma and concomitant nAMD (Figure 1). In addition, although both glaucoma and nAMD are commonly treated diseases, obtaining a larger case–control study population seems challenging because of the small overlap of patients with both diseases. A considerably longer follow-up time does not seem easily achievable either because of the typically advanced age of patients with nAMD and increasing the rate of VF testing is not possible when collecting Real World Data. However, in

spite of our small sample size of 37 patients, we found a statistically significant difference in VF progression rates between nAMD treated glaucoma patients compared to their controls (Table 1). Continuing accumulation of real-world data at additional clinical centres may shed further light on these questions.

Fortunately, glaucoma and nAMD requiring repeated intravitreal anti-VEGF injections do not commonly occur in the same patient. When they do occur concomitantly and obviously nAMD requires active treatment, the impact of IOP spiking on glaucoma progression needs to be carefully considered.

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ETHICAL APPROVAL

The retrospective, registry-based study was approved by the administration of the Tampere University Hospital (R21519/2021). The study was conducted in accordance with the Declaration of Helsinki.

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