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Outcome of anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration in real-life setting

Maria Kataja,^{1,2} Pekko Hujanen,¹ Heini Huhtala,³ Kai Kaarniranta,^{4,5} Anja Tuulonen,¹ Hannele Uusitalo-Jarvinen^{1,2}

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¹Tays Eye Centre, Tampere University Hospital, Tampere, Finland

²Department of Ophthalmology, University of Tampere, Tampere, Finland

³School of Health Sciences, University of Tampere, Tampere, Finland

⁴Department of Ophthalmology, University of Eastern Finland, Kuopio, Finland

⁵Department of Ophthalmology, Kuopio University Hospital, Kuopio, Finland

Correspondence to

Dr Hannele Uusitalo-Jarvinen, Tays Eye Centre, Tampere University Hospital Tampere, 33521 Tampere, Finland; llhausu@uta.fi

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ABSTRACT

Aims To evaluate outcome of anti-vascular endothelial growth factor (VEGF) therapy for the treatment of neovascular age-related macular degeneration (nAMD) in the real-life setting and to compare incidence of ocular serious adverse events (SAE) after injections administered by nurses and physicians.

Methods Retrospective, single-centre study. Medical records of patients receiving anti-VEGF treatment for nAMD between 2008 and 2013 with three-loading-dose regimen were evaluated. Outcome measures were baseline visual acuity (VA), change in VA, number of intravitreal injections, incidence of ocular SAE and patients' baseline characteristics affecting VA change. In addition, the number of injections per 1000 citizens living in the serving area and per individuals over 65 years old were estimated.

Results 1349 eyes in 1117 patients received a total of 11 562 intravitreal anti-VEGF injections. Twenty-one per cent of patients received treatment for both eyes. The mean baseline Snellen VA was 0.32. The mean change of VA from baseline was +2, +2 and ± 0 Early Treatment Diabetic Retinopathy Study letters and the mean numbers of injections were 5.7, 4.7 and 4.9 at years 1, 2 and 3, respectively. There was a negative correlation between baseline VA and change of VA. Incidence of endophthalmitis was 0.086%. No difference in the incidence of ocular SAE was identified between injections given by nurses or by physicians. The number of intravitreal injections per all citizens was 9 per 1000 inhabitants and 45 per 1000 inhabitants over 65 years.

Conclusion The VA was maintained at the baseline level (± 0 letters) with the mean of 15.3 anti-VEGF injections in real-world clinical practice during 3-year follow-up.

INTRODUCTION

The development of vascular endothelial growth factor (VEGF) inhibitors has revolutionised the course of neovascular age-related macular degeneration (nAMD) by providing therapy to decelerate or even halt the progression of the disease.¹ Four intraocular anti-VEGFs have been used: ranibizumab (Lucentis, Genentech, San Francisco, California, USA), aflibercept (Eylea, Regeneron Pharmaceuticals, Tarrytown, New York, USA) and pegaptanib sodium (Macugen, Eyetech Pharmaceuticals/Pfizer, New York, USA) are registered for intraocular use, while bevacizumab (Avastin, Genentech) is widely used as an off-label drug in the treatment of nAMD.

Pegaptanib was the first VEGF inhibitor approved for use in nAMD. However, patients experienced visual decline² and pegaptanib use decreased after the more effective anti-VEGFs became available. Bevacizumab and ranibizumab have been shown to have similar efficacy and safety profiles in several randomised controlled trials (RCTs).^{3–7} Aflibercept has been shown to result in visual outcomes similar to ranibizumab.^{8,9}

Fixed monthly ranibizumab and bevacizumab and bimonthly aflibercept (after 3 monthly injections) as well as pro re nata (PRN) regimen have resulted in visual acuity (VA) gain of 6–11 Early Treatment Diabetic Retinopathy Study (ETDRS) letters at 2-year follow-up in RCTs.^{3–11} Less frequent monitoring and injections, in turn, have provoked deterioration of outcome.^{12,13}

The strict selection criteria in RCTs restrict their extrapolation to everyday practice: monthly clinic visits strain patients and healthcare providers, sometimes leading to infrequent treatment regimen. Understanding the real-world outcomes is essential to improve the therapy and to reduce overall costs. Recently, the Neovascular Age-Related Macular Degeneration Database study showed VA changes of +2, +1 and –2 ETDRS letters from baseline at years 1–3, and the AURA (Anti-vascular endothelial growth factor treatment Regimens in patients with wet Age-related macular degeneration) study +2.4 and +0.6 letters at years 1–2, respectively.^{14,15}

In the present study, the outcomes of anti-VEGF therapy for nAMD, the incidence rate of ocular severe adverse events (SAEs) after injections administered by nurses and by physicians and the number of annual injections per 1000 citizens and per 1000 over 65-year-old citizens were assessed in real-life setting.

MATERIALS AND METHODS

Study design

A retrospective study was conducted in Tays Eye Centre (Tampere University Hospital, Finland). The anti-VEGF treatment protocol was modified PRN: outcome assessment after a loading dose of three intravitreal injections, and in case of inadequate therapeutic response or reactivations, treatment continuation with 3–6 injections. The injection and/or monitoring visits took place every 6–8 weeks until November 2011 and thereafter every 4–6 weeks. The treatment criterion was VA ≥ 0.1 .



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Nevertheless, the ophthalmologists were allowed to deviate from the protocol based on their own clinical judgement.

The electronic medical records of Tampere University Hospital were searched for all patients with International Classification of Diseases 10th Revision code for nAMD (H35.31) and ≥ 1 The Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NCSP) code for intravitreal injection (CKD05) between 1 January 2008 and 31 December 2013. The study was restricted to treatment-naïve eyes undergoing monotherapy with ≥ 1 anti-VEGF injection for nAMD during the above-mentioned period (see online supplementary figure 1). Switching between anti-VEGF compounds was allowed. Exclusion criteria were treatment initiation before 2008, anti-VEGF injection for other reasons than nAMD and use of laser photocoagulation, photodynamic therapy or intravitreal steroid.

As this study was retrospective in nature and patient identifiers were stripped out completely after the data collection, the ethics committee of Pirkanmaa Hospital District determined that formal ethics approval was not required. The study was conducted in accordance with the Declaration of Helsinki.

Data collection

A pilot study was conducted on patients with birthday divisible by 5 ($n=203$), whereafter the data collection expanded to cover the entire study population. For the studied eyes, data were collected from diagnosis date to end of treatment and/or monitoring or until 31 December 2013, including intravitreal injection and monitoring visits and ocular SAEs (endophthalmitis, retinal detachment or traumatic cataract). Fellow eyes with VA ≥ 0.1 and no prior nAMD treatment were identified (excluding the pilot study group) for the analysis of nAMD incidence in the second eye.

VA is reported as Snellen unless otherwise stated, measured using refraction, habitual correction, pinhole or a combination. For comparison to previous studies, Snellen to ETDRS conversion was done using the formula $85+50 \cdot \log(\text{Snellen fraction})$ (described previously).¹⁶ Very low VA measurements were analysed by substituting counting fingers with 0.025 and hand movements or light perception with 0.01.

Outcome measures

The main outcome measure was VA change at 1, 2 and 3 years from baseline. Other outcome measures were baseline characteristics affecting VA change, number of intravitreal injections given each treatment year, number of injections given by nurses and by physicians, incidence of SAEs, number of different anti-VEGFs used and nAMD incidence in the second eye. In addition,

the numbers of injections per 1000 citizens and per 1000 over 65-year-old citizens living in Pirkanmaa Hospital District were estimated.

Statistical methods

The overall study population consisted of patients that received ≥ 1 anti-VEGF injection. The effectiveness analysis sets consisted of eyes with completed follow-up of 1, 2 and 3 years. Snellen VA was used as a continuous variable. To account for missing data, Last-Observation-Carried-Forward (LOCF) analysis was used. If there was no VA available from the visit of treatment decision, the baseline VA was taken from a prior visit within 1 month, or secondarily from the first injection visit if available.

RESULTS

Baseline characteristics

The baseline characteristics are presented in table 1. During the 6-year study period, 1349 eyes in 1117 patients were treated with 11562 intravitreal anti-VEGF injections. Of these patients, 232 (21%) received treatment for both eyes. Within 2 years of first eye nAMD diagnosis, 18% received treatment also for the second eye (see online supplementary figure 2).

Female preponderance of the patients was 2.2:1 and 1.9:1 after adjusting for national data for sex ratios in people over 50 years. The number of eyes entered into the study doubled from 2008 to 2013 (table 2). Mean baseline VA was lower in the first treated eyes than in the second treated (0.30 vs 0.42) and increased from 0.29 in 2008 to 0.35 in 2013. Most eyes did not meet the European Union (EU) driving standards (baseline VA ≥ 0.5).

The population of Pirkanmaa Hospital District was 497 002 in 31 December 2013, of whom 19.2% (95 424) were ≥ 65 year olds (Finnish Statistics of Medicines 2013). The number of injections in 2013 was 9 per 1000 inhabitants and 45 per 1000 ≥ 65 -year-old inhabitants living in the serving area.

Intravitreal injections

Altogether, bevacizumab was given in 10884 and ranibizumab in 583 injections (table 3). Bevacizumab was the most commonly used anti-VEGF each year since its introduction in 2009. Ranibizumab use declined rapidly after it was the most common anti-VEGF in 2008 (86%). Pegaptanib was used only until 2009 and aflibercept only during 2013. While physicians performed all injections in 2008, already in 2012, nurses performed 99% of injections (table 3).

Table 1 Baseline characteristics of the eyes treated for AMD in 2008–2013 in Tays Eye Centre

	First treated eye (n=1117)	Second treated eye (n=232)	All eyes (n=1349)
Age (years), median (IQR)	80 (74–84)	81 (77–85)	80 (75–84)
Female sex, n (%)	765 (68)	179 (77)	944 (70)
Baseline VA*, mean (SD)	0.30 (0.21)	0.42 (0.24)	0.32 (0.22)
Baseline VA*, n (%)			
<0.3	589 (53)	72 (31)	661 (49)
0.3 – <0.5	297 (27)	75 (32)	372 (28)
0.5 – <0.8	197 (18)	62 (27)	259 (19)
≥ 0.8	32 (3)	21 (9)	53 (4)
Missing	2 (0)	2 (1)	4 (0)

*Snellen VA.

AMD, age-related macular degeneration; VA, visual acuity.

Table 2 Mean change of VA from baseline and number of intravitreal injections per eye

	Baseline VA										First year completers										Second year completers										Third year completers																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																	
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*Last Observation-Carried-Forward analysis; VA, change from baseline.
Correlation between baseline VA and VA change: Spearman's two-tailed $p=-0.283$, $p=-0.476$ and $p=-0.525$ at years 1–3, respectively; all p 's <0.001.
ETDRS, Early Treatment Diabetic Retinopathy Study; IVI, intravitreal injections; NA, not available; VA, visual acuity.

Table 3 Distribution of injections by compound, administrator and by year

	Year													
	2008		2009		2010		2011		2012		2013		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Anti-VEGF														
Bevacizumab	0	0	807	84	1367	100	1791	100	2671	99	4248	98	10884	94
Ranibizumab	361	86	127	13	1	0.1	2	0.1	16	0.6	76	2	583	5
Pegaptanib sodium	59	14	30	3	0	0	0	0	0	0	0	0	89	0.8
Aflibercept	0	0	0	0	0	0	0	0	0	0	6	0.1	6	0.1
Total	420	100	964	100	1368	100	1793	100	2687	100	4330	100	11562	100
Administrator														
Physician	420	100	961	100	260	19	74	4.1	21	0.8	77	1.8	1813	16
Nurse	0	0	3	0.3	1108	81	1719	96	2665	99	4251	98	9746	84
NA	0	0	0	0	0	0	0	0	1	0	2	0	3	0
Total	420	100	964	100	1368	100	1793	100	2687	100	4330	100	11562	100

NA, not available; VEGF, vascular endothelial growth factor.

The mean numbers of injections were 5.7, 4.7 and 4.9 during completed treatment years 1–3, respectively (table 2). During the study period, the number of injections given during the first year increased gradually (4.9 injections in eyes first treated in 2008 to 6.8 in 2012). Similar increase was observed for years 2–3.

Change of VA from baseline

Change of VA from baseline at 1, 2 and 3 years was analysed for eyes that completed respective follow-ups (Effectiveness analysis sets; LOCF analysis). The change from baseline was +2, +2 and ± 0 ETDRS letters at years 1–3, respectively (table 2). Completing the yearly follow-ups was equally common for the first and second treated eyes, although the first appeared to retain their VA slightly better. Treatment initiation year did not affect the change of VA.

The largest benefit was seen in patients with low baseline VA (figure 1, table 2). In the eyes with baseline VA <0.3 , there was an increase of 14 letters at 3 years. In contrast, VA appeared to decline in eyes with baseline VA ≥ 0.3 : the better the baseline VA, the bigger the observed decline. There was an increasingly negative correlation between baseline VA and change of VA from baseline (table 2). In contrast, neither gender nor baseline age were shown to have a statistically significant association with change of VA from baseline.

As clinical trials have strict inclusion criteria for baseline VA that is associated with VA gain, subgroup analyses were made to test whether implementing these would affect the visual outcomes in the present study. In the present study, 947 eyes (70%) met the inclusion criteria, best corrected visual acuity 0.065–0.5 Snellen equivalent, of the pivotal clinical trials of ranibizumab and aflibercept (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA), Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR), Vascular Endothelial Growth Factor VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (VIEW)).^{9–11} In this subgroup, mean baseline Snellen VA was 0.28 equalling to 58 ETDRS letters and VA change was +4, +5 and +4 letters at years 1–3, respectively (table 4). Implementing the inclusion criteria of The Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) study,³ 1146 eyes (85%) had Snellen VA 0.065–0.8. Mean baseline was 0.35 (62 letters), and

change at years 1–3 was +2, +2 and ± 0 letters. The injection frequency and baseline age of both subgroups were similar to the whole study population (table 4).

Serious adverse events

The incidence of ocular SAEs was 0.104% (12/11562 injections), including 10 endophthalmitis (0.086%), two retinal detachments (0.017%) and no traumatic cataracts. There was no statistically significant difference in the incidence of SAEs after injections given by nurses (10 per 9746 injections, 0.103%) or physicians (2 per 1813, 0.110%) ($p=0.93$).

After the treatment of endophthalmitis, VA turned out at least at the same level it was before the endophthalmitis in seven out of 10 eyes. In the remaining three eyes with endophthalmitis, VA remained at a lower level than before the endophthalmitis (Snellen VA declining from 0.4 to 0.25, from 0.25 to counting fingers and 0.05 to counting fingers, respectively).

Treatment and follow-up discontinuation

The treatment and follow-up was discontinued before the end of 2013 in half of all cases ($n=654$). The reason was poor treatment response in 47% of those and disease inactivation in 27% (figure 1). Other reasons were worsening of overall health status (8%), patient declined treatment (8%), death within 1 month (3.2%) and other/unknown (8%).

Discontinuation for any reason occurred most often in the baseline VA <0.3 group (61%, $n=402$). In eyes with baseline VA $0.3-<0.5$, $0.5-<0.8$ and ≥ 0.8 , the rate varied between 36% and 38%. Moreover, the follow-up of eyes with baseline VA <0.3 was more often discontinued due to poor treatment response (61%) than that of eyes with baseline VA ≥ 0.3 (between 21% and 26% in each group). In groups with baseline VA >0.3 , disease inactivation was more frequent than poor treatment result (figure 1). In the lowest baseline VA group, discontinuation occurred over threefold more frequently from poor treatment response compared with disease inactivation (243 vs 64).

DISCUSSION

This retrospective study shows the anti-VEGF treatment for nAMD using modified PRN regimen and mostly bevacizumab (94%) resulting in stabilisation of VA for at least 3 years in real-life setting. Although VA was maintained, the initial gain was lower than in clinical trials with fixed monthly treatment and/

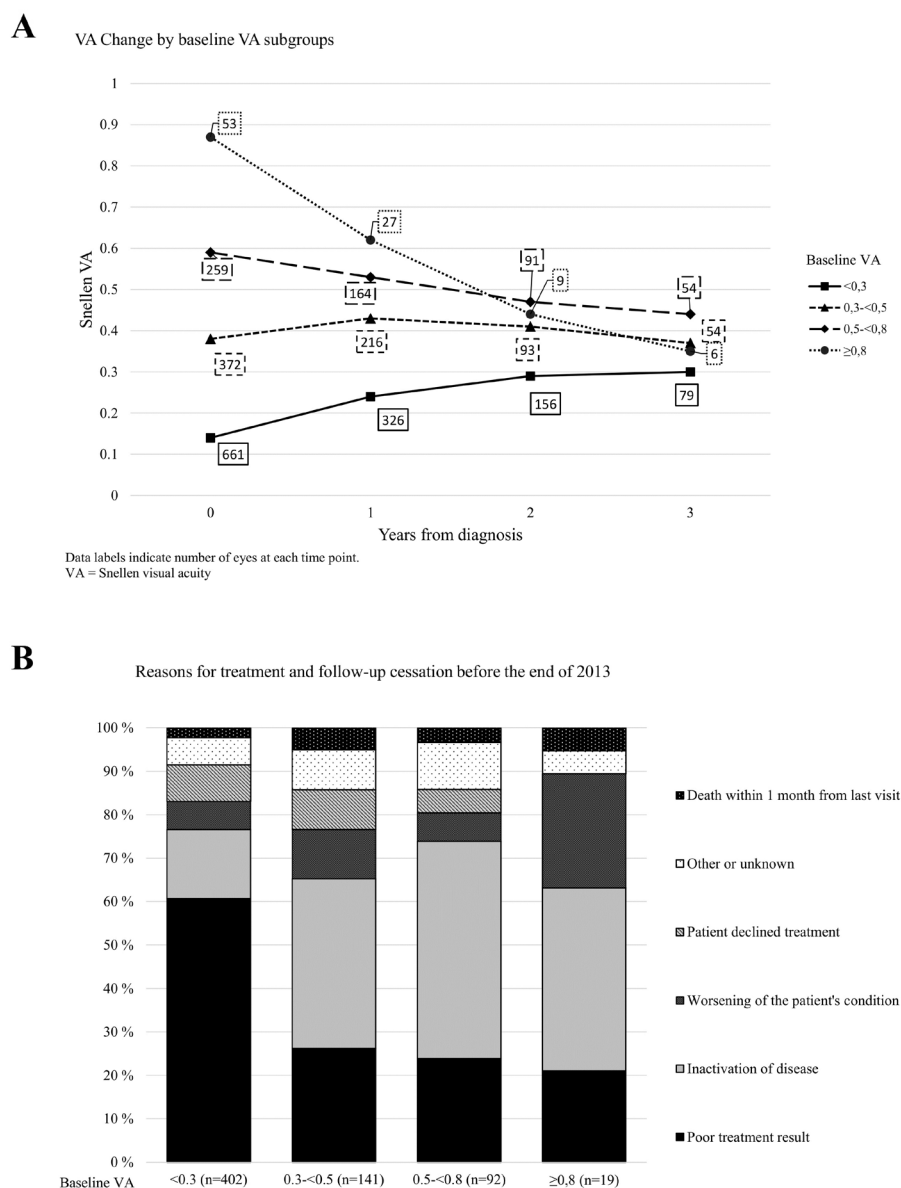


Figure 1 (A) Graph showing mean visual acuity (VA) and number of eyes over time in subgroups of different baseline VA. Snellen VA at baseline and at 1, 2 and 3 years stratified by baseline VA. (B) Reasons for treatment and follow-up cessation before the end of 2013 in subgroups of eyes with baseline Snellen VA <0.3, 0.3-0.5, 0.5-0.8 and ≥0.8.

or monitoring.^{3 9-11} However, the visual outcome was in accordance with previous real-life studies.^{14 15 17} Poor VA gain has been associated with low injection and monitoring frequency.^{18 19} Protocols of clinical trials have proven challenging to follow in practice; the injection frequency in the previous real-life studies^{14 15 17} as well as in the present study were lower than in clinical trials.

Mean baseline VA and age were higher than in most clinical trials,^{3 9-11} both known to be associated with VA gain.^{14 18} In the present study, negative correlation was confirmed for baseline VA although not for age. The poor VA gain in eyes with good baseline VA may originate from a ceiling effect.

In the subgroup of eyes that met the criteria of MARINA, ANCHOR and VIEW,⁹⁻¹¹ mean baseline VA was lower compared with the whole study population, although slightly higher than in these trials (table 4). There was a clear VA gain, although slighter than in clinical trials. Implementing the inclusion criteria of CATT³ in the present study, mean baseline VA was higher than that of whole study population or CATT bevacizumab PRN treatment arm, but the mean change from baseline remained unchanged.

Tays Eye Centre was the first hospital in Finland and among the first ones internationally to train nurses to give intravitreal injections. Initiated in 2009, this practice was soon adopted as

Table 4 Visual outcomes and number of injections in anti-VEGF treatment studies

Study	Baseline			Year 1			Year 2			Year 3		
	n	Age (years)	VA*	n	Change of VA*†	IVI	n	Change of VA*†	IVI	n	Change of VA*†	IVI
MARINA‡	77		54		+7	monthly		+7	monthly		NA	NA
ANCHOR‡	76		47		+11	11.2		+11	10.1		NA	NA
VIEW studies§	76		54		+8	7.5		+8	3.6		NA	NA
CATT¶	79		60		+6	7.7		+5	6.4		NA	NA
AURA	77		55		+2	5		+1	2.2		NA	NA
Tufail <i>et al</i> 2014	79		55		+2	5		+1	4		-2	4
Current study¶**												
All eyes	1345	80	60	733	+2	5.7	349	+2	4.7	193	±0	4.9
Baseline VA 0.065–0.5	947	80	58	539	+4	5.8	245	+5	4.8	131	+4	5.0
Baseline VA 0.065–0.8	1146	80	62	663	+2	5.7	314	+2	4.7	173	±0	5.0

*All VA scores in Early Treatment Diabetic Retinopathy Study letters IVI.

†Change of VA from baseline.

‡Ranibizumab 0.5 mg monthly treatment arm (Brown *et al* 2006; Rosenfeld *et al* 2006).

§Aflibercept treatment arm (Heier *et al* 2012).

¶Bevacizumab pro re nata treatment arm (Martin *et al* 2011).

**Last-Observation-Carried-Forward analysis.

IVI, intravitreal injections; NA, not available; VA, visual acuity.

routine: nurses administered 81%–99% of injections per year in 2010–2013. There was also a rapid shift from using ranibizumab to bevacizumab and an increase in injection frequency during the study period. Yet the VA change from baseline remained similar, even though a correlation between visual outcome and injections frequency has been previously observed.¹⁵ However, this discrepancy may relate to the inverse association between VA change and baseline VA, and the simultaneous increase in injections frequency and baseline VA. The increase in baseline VA may refer to treatment initiation at earlier stage of nAMD towards the end of the study period. This, in turn, may indicate increased awareness of treatment availability resulting in patients seeking treatment earlier or faster diagnosing after the onset of symptoms.

Treatment discontinuation rates have been shown to be high in real-life clinical practice.^{14 15 17 20} The proportion of eyes lost to follow-up was 47% in AURA study at year 2 and 78% in the Neovascular Age Related Macular Degeneration Database study at year 3.^{14 15} In the USA, discontinuation rates among Medicare beneficiaries were 57% and 71% within 12 and 24 months, respectively.²⁰ In the present study, follow-up was discontinued in 48% of the eyes before the end of 2013, the rate being highest in eyes with baseline VA <0.3 (61%; subgroups with VA ≥0.3, 36–38%). The most common reason was poor treatment response in eyes with baseline VA <0.3 and inactivation of disease in other VA groups. This suggests that early treatment initiation leads more likely to inactivation of nAMD. On the other hand, the eyes that were diagnosed at rather progressive stage (VA <0.3) and continued in treatment had the biggest VA increase from baseline. These patients are likely to appreciate the treatment even when the progression of the disease is slowed down or halted, retaining at least part of their vision.

The introduction of anti-VEGF injections for nAMD has placed a sudden and extensive treatment burden on healthcare systems. In Tays Eye Centre, the number of injections increased 10-fold from 2008 to 2013. Injections by nurses were introduced in 2009 to provide treatment for all patients in need. Our retrospective analysis shows that this change in policy did not change the incidence of SAEs, which is in accordance with previous reports.^{21 22} Furthermore, the present study indicated no difference in VA

change related to injections given by physicians or nurses, nor related to the use of ranibizumab or bevacizumab.

In Finland, bevacizumab is the most commonly used anti-VEGF drug for nAMD due to its affordability. The present study outcome may be considered a real-life outcome of bevacizumab in nAMD, as bevacizumab accounted for 94% of injections. This suggests that VA outcomes of bevacizumab and ranibizumab are similar also in real-life clinical practice in a large, unselected patient population. The PRN treatment protocol appears more cost-effective than monthly bevacizumab, as small increases in effects incur higher additional costs.²³ Furthermore, bevacizumab appears more cost-effective than ranibizumab and aflibercept given as needed or monthly.²³

Previously, numbers of nAMD injections per total population or per population of ≥65 year olds have been scarcely reported. For 2011, the number of injections in southern Finland (using mainly bevacizumab) was twofold to threefold higher than that in southern Sweden (using ranibizumab).²⁴ The Swedish Medical Retina experts assumed that the difference originates from stricter indications for initiating nAMD treatment. It is unlikely that the nAMD prevalence would vary twofold to threefold in neighbouring Nordic countries. In the USA, the rate of fee-for-service Medicare beneficiaries aged ≥65 years receiving intravitreal injections varied by sevenfold across states, ranging from 4/1000 (Wyoming) to 28/1000 (Utah), average 19/1000.²⁵ In the present study, in 2013, the number of intravitreal injections for nAMD per population living in the serving area was 9/1000 inhabitants and 45/1000 inhabitants aged ≥65 years, which is over twofold higher than that reported in the USA.

The efficacy of anti-VEGF treatment in nAMD has been shown in several RCTs.^{3–6 8–11} Although RCTs are the gold standard for evaluating outcomes of medical interventions, their strictly defined study populations may not include all the patients that would actually receive the drug in clinical practice, and the standardised conditions often differ from real-life settings. Due to these discrepancies in patient selection, treatment conditions and regimens, both the effectiveness and potential risks/side effects of the therapy may be different and, thus, the results of RCTs may not be directly translated into decision making in clinical practice. The present retrospective study shows stabilisation of

VA in response to anti-VEGF therapy, although with substantially lower numbers of annual anti-VEGF injections than in RCTs.

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Competing interests HUJ: Advisory Board/Consultant (Allergan, Bayer, Novartis); Speaker's Bureau (Santen).

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval Pirkanmaa Hospital District Ethical Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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