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-Jarvinen1,2

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. Four intravitreal 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 decline 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). Aflibercept has been shown to result in visual outcomes similar to ranibizumab.

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. Less frequent monitoring and injections, in turn, have provoked deterioration of outcome.

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.

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.
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 anti-VEGF injection or light perception with 0.01. 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 photoacoagulation, 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 $85+50\log10(\text{Snellen fraction})$ (described previously). 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

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

*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

| Treatment starting year | 2008 | 152 | 11 | 0.29 | 0.21 | 58 | 115 | 0.32 | 0.34 | 0.22 | +2 | 4.9 | 1.6 | 68 | 0.33 | 0.36 | 0.24 | +2 | 3.7 | 2.2 | 50 | 0.36 | 0.33 | 0.22 | −2 | 3.6 | 2.4 |
|------------------------|------|-----|-----|-------|------|-----|-----|------|-------|------|-----|-----|-----|-----|------|-------|-----|-----|-----|-----|------|-------|-----|-----|-----|-----|------|-------|-----|
|                        | 2009 | 173 | 13 | 0.29 | 0.20 | 58 | 113 | 0.33 | 0.38 | 0.24 | +3 | 5.2 | 1.3 | 76 | 0.36 | 0.39 | 0.23 | +2 | 4.5 | 2.2 | 58 | 0.34 | 0.35 | 0.23 | +1 | 4.1 | 2.3 |
|                        | 2010 | 192 | 15 | 0.32 | 0.21 | 60 | 154 | 0.34 | 0.35 | 0.22 | +1 | 5.5 | 1.5 | 111 | 0.36 | 0.36 | 0.20 | +2 | 4.5 | 2.0 | 85 | 0.39 | 0.38 | 0.22 | −1 | 6.3 | 2.7 |
|                        | 2011 | 219 | 16 | 0.30 | 0.22 | 59 | 157 | 0.33 | 0.37 | 0.25 | +3 | 5.5 | 1.4 | 94 | 0.34 | 0.38 | 0.24 | +3 | 5.9 | 2.5 | 0 | NA | NA | NA | NA | NA |
|                        | 2012 | 267 | 21 | 0.34 | 0.22 | 61 | 194 | 0.38 | 0.41 | 0.25 | +1 | 6.8 | 1.9 | 0 | NA | NA | NA | NA | NA | 0 | NA | NA | NA | NA |
|                        | 2013 | 317 | 26 | 0.35 | 0.22 | 62 | 238 | 0.38 | 0.44 | 0.27 | −1 | 7.0 | 1.9 | 0 | NA | NA | NA | NA | NA | 0 | NA | NA | NA | NA |

| Baseline VA | ≤0.3 | 661 | 49 | 0.14 | 0.08 | 42 | 326 | 0.15 | 0.24 | 0.18 | +10 | 5.6 | 1.6 | 156 | 0.15 | 0.29 | 0.21 | +14 | 4.9 | 2.2 | 79 | 0.15 | 0.30 | 0.22 | +14 | 4.7 | 2.8 |
|             | 0.3 to 0.5 | 372 | 28 | 0.38 | 0.05 | 64 | 216 | 0.38 | 0.43 | 0.20 | +3 | 5.9 | 1.8 | 93 | 0.38 | 0.41 | 0.21 | +2 | 4.7 | 2.4 | 54 | 0.38 | 0.37 | 0.21 | −1 | 5.3 | 2.7 |
|             | 0.5 to 0.8 | 259 | 19 | 0.59 | 0.09 | 74 | 164 | 0.59 | 0.53 | 0.23 | −2 | 5.5 | 1.7 | 91 | 0.60 | 0.47 | 0.22 | −5 | 4.2 | 2.5 | 54 | 0.61 | 0.44 | 0.24 | −7 | 4.9 | 2.9 |
|             | ≥0.8 | 53 | 4 | 0.87 | 0.08 | 82 | 27 | 0.85 | 0.62 | 0.26 | −7 | 6.4 | 1.6 | 9 | 0.88 | 0.44 | 0.26 | −15 | 5.6 | 2.2 | 0 | 0.89 | 0.35 | 0.27 | −21 | 5.0 | 1.9 |

*Last-Observation-Carried-Forward analysis of VA change from baseline.
Correlation between baseline VA and VA change: Spearman’s two-tailed $\rho = −0.283, \rho = −0.476$ and $\rho = −0.525$ 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.
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, and 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)).

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, 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 endophthalmites (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...
Clinical science

Mean baseline VA and age were higher than in most clinical trials,\textsuperscript{3-11} both known to be associated with VA gain.\textsuperscript{14-19} 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,\textsuperscript{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 CATT\textsuperscript{3} 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

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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.
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, unselicted patient population. The PRN treatment protocol appears more cost-effective than monthly bevacizumab, as small increases in effects incur higher additional costs. Furthermore, bevacizumab appears more cost-effective than ranibizumab and aflibercept given as needed or monthly.

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). 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. 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. 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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Age (years)</td>
<td>VA*</td>
<td>n</td>
</tr>
<tr>
<td>MARINA†</td>
<td>77</td>
<td>54</td>
<td>+7</td>
<td>monthly</td>
</tr>
<tr>
<td>ANCHOR‡</td>
<td>76</td>
<td>47</td>
<td>+11</td>
<td>11.2</td>
</tr>
<tr>
<td>VIEW studies§</td>
<td>76</td>
<td>54</td>
<td>+8</td>
<td>7.5</td>
</tr>
<tr>
<td>CAT¶</td>
<td>79</td>
<td>60</td>
<td>+6</td>
<td>7.7</td>
</tr>
<tr>
<td>AURA</td>
<td>77</td>
<td>55</td>
<td>+2</td>
<td>5</td>
</tr>
<tr>
<td>Tufail et al 2014</td>
<td>79</td>
<td>55</td>
<td>+2</td>
<td>5</td>
</tr>
<tr>
<td>Current study**</td>
<td>All eyes</td>
<td>1345</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Baseline VA 0.065–0.5</td>
<td>947</td>
<td>80</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Baseline VA 0.065–0.8</td>
<td>1146</td>
<td>80</td>
<td>62</td>
</tr>
</tbody>
</table>

* 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.
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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Contributors. HUJ and AT designed the research. MK and PH performed the data collection. MK, PH, HH, HUJ and KK analysed the data. MK, KK, AT and HUJ wrote the manuscript. MK made the figures. MK, PH, HH, KK, AT and HUJ reviewed the paper.

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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.

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