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Reduced occurrence of severe visual impairment after introduction of anti-Vascular Endothelial Growth Factor in wet age-related macular degeneration – a population- and register-based study from northern Sweden

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ABSTRACT.

Purpose: **To study the occurrence of severe visual impairment (SVI) and treatment outcome at 12 months in patients treated for wet age-related macular degeneration (AMD) by use of data from the Swedish Macula Register (SMR) and referrals to the regional low vision clinics in five northern counties.**

Methods: **Referrals to low vision clinics during 2005, 2009 and 2013 and treatment outcome at 12 months from the SMR database from 2008 until 2013 in patients >65 years of age in five northern counties were included in the survey.**

Results: **The rate of referral due to AMD was significantly reduced during the time period (−48%; $p < 0.001$). At 12 months, a significant slight mean improvement in logMAR visual acuity (VA) was observed (−0.01, SD 0.37; $p < 0.001$) after a mean of 5.0 ± 2.3 anti-vascular endothelial growth factor (VEGF)-injections were administered. Age and low baseline VA was associated with less favourable visual outcome ($p < 0.001$).**

Conclusion: **Referral rate to low vision clinic is a valuable tool for estimating occurrence of SVI and fell between the years 2005 until 2013. Data from the SMR showed improvement in visual acuity on the whole, but also identified patients at high risk for developing SVI during anti-VEGF-treatment.**

Key words: anti-vascular endothelial growth factor – low vision clinics – Swedish Macula Register – wet AMD

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Introduction

Age-related macular degeneration (AMD) is the most frequent cause of severe visual impairment in the western world (Friedman et al. 2004; Bourne et al. 2014) and the prevalence is projected to increase with increasing age of the population (Lindekleiv & Erke 2013). Visual impairment due to bilateral AMD is associated with significantly reduced quality of life and increased need for assistance related to daily activities (Soubrane et al. 2007).

Treatment for neovascular wet AMD with anti-vascular endothelial growth factor (VEGF) drugs was established in 2006 (Rosenfeld et al. 2006). Repeated and frequent intravitreal administration of anti-VEGF drugs has been shown to improve visual acuity in a majority of eyes (Martin et al. 2011; Heier et al. 2012). In Sweden, anti-VEGF treatment for wet AMD is available for all residents and is fully reimbursed within the public health care system. In 2013, the

number of intravitreal treatments administered in Sweden was approximately 30 000 (Swedish Macula Register 2013). Treatments and treatment outcome are continuously reported in a national quality register, the Swedish Macula Register (SMR) (Swedish Macula Register 2013).

Studies from Denmark (Bloch et al. 2012) and Israel (Skaat et al. 2012) have found a declining incidence of legal blindness due to AMD over the past 10 years coinciding with the introduction of anti-VEGF treatment for wet AMD. A reduced incidence of blindness attributable to wet AMD since 2006 had recently been reported from Scotland (Borooah et al. 2015). It is not known whether a similar trend is present in Sweden.

In Sweden, low vision clinics provide visual rehabilitation in case of severe visual impairment (SVI) defined as visual acuity of the better-seeing eye less than 0.3 (20/70) Snellen, significantly restricted visual fields or presence of homonymous hemianopia. Ophthalmologists are only allowed to refer patients to a low vision clinic. In the present study, information on referrals to low vision clinics was used as a measure of occurrence of SVI in five counties in northern Sweden. Further, data from the SMR were used to evaluate treatment outcome in patients treated for wet AMD from the same region of Sweden.

The aims of the present study were to study the occurrence of SVI in five counties in northern Sweden on the basis of referral to the regional low vision clinic; to evaluate treatment and treatment outcome at 12 months in patients treated for wet AMD from the same regions of the country by use of data from the SMR including investigation of prognostic factors at baseline for referral to low vision clinic after start of treatment for wet AMD.

Materials and Methods

The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Regional Ethical Review Board in Uppsala, Sweden.

Referral to low vision clinic

Occurrence of severe visual impairment in five counties in northern Sweden was assessed on the basis of referral to the regional low vision clinic. Referrals during 3 years were studied in detail - 2005, 2009 and 2013. Patients 65 years of age and older were included in the survey. Information regarding the main reason for referral to low vision clinic was obtained from patient medical records. In three clinics, no formal referrals were made and instead, appointments of new patients at the low vision clinic were analysed. Demographic information about the background population was obtained from Statistics Sweden (2015). Rate ratios for referrals were calculated for the total number of referrals and for referrals due to AMD respectively.

Register study

Data from the SMR were used to evaluate treatment and treatment outcome at 12 months in a population of patients from the same area of the country receiving anti-VEGF treatment for wet AMD. Prognostic factors at baseline for subsequent referral to low vision clinic after start of treatment for wet AMD were investigated. National coverage of the register in 2012 was 76.2% whereas in the five counties included in this study, register coverage was 84.4% (range 76.2–93.2%; Swedish Macula Register 2013).

The indication for initiating anti-VEGF treatment for wet AMD was reduction in visual acuity in combination with signs of active wet AMD on optical coherence tomography (OCT) and/or fluorescein angiography. Following the initial three monthly anti-VEGF-treatments, further treatment was given as needed (*pro re nata*) based on visual acuity and signs of active wet AMD on OCT. In four counties, ranibizumab initially was first-of-choice anti-VEGF drug and treatment was shifted to bevacizumab in 2011.

The validity of register data from the county hospitals participating in the survey was tested according to register standards. For 39 randomly selected patients, register data were compared to data in the patient medical records. The following variables were included in the validation survey: best corrected visual acuity Early Treatment Diabetic Retinopathy Study protocol (ETDRS), best corrected visual acuity (Snellen), near visual acuity, type of intravitreal drug given, occurrence of treatment-requiring adverse events and number of intravitreal injections given. In total, 3456 individual variables were included in the validation survey. Any discrepancy between register data and data in hospital records was noted and type of discrepancy was analysed.

The register database from Jan 1, 2008 until Dec 31, 2013 for the five counties was obtained to select all new eyes starting anti-VEGF treatment for wet AMD. In total, 1614 eyes were found. In 191 patients, both eyes were started on anti-VEGF treatment after Jan 1, 2008. Only the first treated eye of each patient was included for further analysis. In total, 190 patients had been referred to low vision clinic before the start of anti-VEGF treatment for wet AMD. As the aim of the survey was to investigate the occurrence of new SVI in the population under study, these patients were excluded from further analysis. For 37 patients, there were no follow-up data in the register. In total, 1196 patients were included in the analysis. Age at start of treatment, data on visual acuity in the treated eye (Snellen), visual acuity in the fellow eye (Snellen) and duration of symptoms at baseline before treatment start were obtained from the register. Visual acuity (Snellen) was converted into logMAR-units using the formula $\text{logMAR} = -10 \log(\text{Snellen})$ (Holladay 1997). Visual acuity of hand movements was converted into logMAR 3 and amaurosis was converted into logMAR 4. Duration of symptoms was categorized as 0 to <2 months, ≥2 to <4 months, ≥4 to <6 months and ≥6 months in the register.

Treatment outcome at 12 months for all eyes was analysed based on register data until Dec 31, 2014 with regard to visual acuity and number of anti-VEGF treatments given. Seven hundred and ninety eyes had logMAR visual acuity data 330–420 days after treatment start. In 116 eyes, treatment was continued beyond 12 months although no visual acuity measurement was performed during the 12-month follow-up interval 330–420 days after treatment start. In 144 eyes (144/1196, 12%), treatment was discontinued before 12 month mainly due to poor or stable visual acuity outcome (114) eyes). Further, 146 eyes were lost to follow-up. In total, for 406 eyes, the last observed visual acuity

measurement was therefore carried forward to 12 months (last observation carried forward, LOCF) for analysis. Total follow-up time and number of anti-VEGF treatments given were obtained from the register. Information on referral to low vision clinic at any time-point during follow-up was obtained from patient medical records. Based on bilateral visual acuity at 12 months, number of patients fulfilling criteria for referral but who had not been referred to low vision clinic was noted.

Statistical methods

Rate ratios with 95% confidence intervals were calculated using OpenEPI (Sullivan et al. 2009). The population at risk was defined as the number of persons aged 65 years or older living in the counties included in the investigation on December 31 in a given year.

SPSS 22 (IBM Corporation, Armonk, NY, USA) was used for the statistical analyses. Start of treatment was considered as baseline. Student's *t*-test for independent samples was used for comparisons of baseline data. Logistic regression analysis of probability for referral to low vision clinic adjusted for age, visual acuity in treated eye, visual acuity in fellow eye and duration of symptoms at baseline was performed. For treatment outcome, unpaired Student's *t*-test was applied for normally distributed data whereas for other data non-parametric Mann–Whitney *U*-test for independent samples was applied. Sensitivity analysis using linear regression adjusted for age and number of intravitreal injections was also performed.

Results

Referral to low vision clinic

During the investigated period, there was an increase in the population aged 65 or older (Table 1). The rate of referral to low vision clinic for all diagnoses was significantly reduced 2013 compared to 2005 (−46%; $p < 0.001$). The rate of referral due to AMD was significantly reduced to a similar extent (−48%; $p < 0.001$). Referral rate for all diagnoses per 100 000 inhabitants 65 years or older declined between 2005 and 2013 (Fig. 1). Referral rates for AMD and for diagnoses other than AMD were similarly reduced. Rate ratio for all diagnoses was 0.53 (CI_{95} 0.48–0.59), for wet AMD 0.52 (CI_{95} 0.45–0.59) and for diagnoses other than AMD 0.56 (CI_{95} 0.48–0.66). Overlapping CI_{95} strongly indicates that the extent of reduction was not significantly different between all diagnoses and referrals due to AMD.

Table 1. Population and number of referrals during 2005, 2009 and 2013 in the investigated counties.

	2005	2009	2013
Population >65 years of age	164 265	174 569	191 523
Referrals (total, no)	961	773	599
Referrals due to AMD (no)	587	494	355
Referrals due to other causes (no)	374	279	244

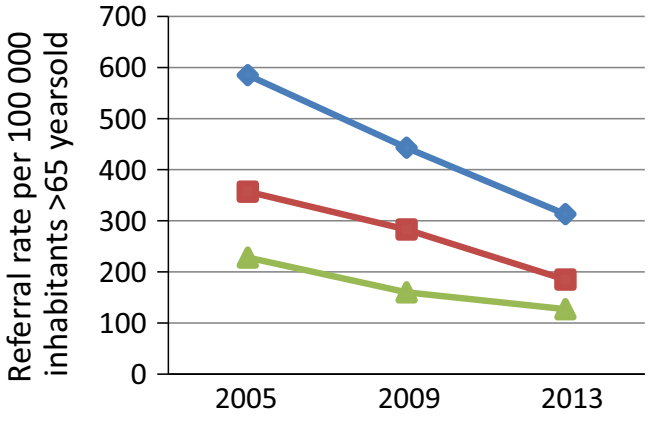

Fig. 1. Referral rates per 100 000 inhabitants 65 years and older: ◆ all diagnoses; ■ AMD; ▲ diagnoses other than AMD.

Validation results

In the validation survey comprising 3456 individual variables, 146 (4.2%) discrepancies between register data and hospital patient records were found. Twenty-four errors (16.4%) concerned registration of near visual acuity. This variable was not included for analysis in the present study. Overall, the number of discrepancies was low and was found not to have an impact on results of the present survey. Register data were considered reliable and were used for further analysis.

Baseline and follow-up

Baseline characteristics and follow-up data were obtained for 1196 eyes in 1196 patients who started anti-VEGF treatment for wet AMD Jan 1, 2008 until Dec 31, 2013. There were 434 men (36%) and 762 women (64%) in the cohort. Mean age of all patients was 77.3 ± 7.9 years. Mean age of men was 77.2 ± 8.2 and of women was 77.2 ± 7.3 years. Mean visual acuity was 0.56 ± 0.28 logMAR corresponding to approximately Snellen 0.25 (20/70). Mean visual acuity in fellow eye was 0.68 ± 0.89 logMAR. Mean total follow-up time was 2 ± 1.5 years (median 1.6 years, range 0–7 years).

For follow-up data at 12 months, data until Dec 31, 2014 from the SMR were evaluated. At 12 months, a significant slight mean improvement in logMAR visual acuity was observed (−0.01 ± 0.37; $p < 0.001$) compared to treatment start. A mean of 5.0 ± 2.3 anti-VEGF-injections were administered during the first treatment year.

Prognostic factors for referral to low vision clinic

Patients with visual acuity Snellen 0.3 or less (<20/70) in the better eye are entitled to referral to low vision clinic for visual rehabilitation. In total 404 of the 1196 patients (34%) had been referred to low vision clinic after treatment start (severe visual impairment group, SVI-group) whereas 792 patients (66%) had not been referred (non-SVI-group).

Table 2. Age, visual acuity in treated eye (logMAR) and in the fellow eye (logMAR), respectively, at treatment start in patients subsequently developing severe visual impairment (SVI-group) compared to in patients without subsequent severe visual impairment (non-SVI-group; Student's *t*-test for unpaired data).

	Group	*N*	Mean	SD	p-Value
Age	SVI	404	80.1	7.0	<0.001
	Non-SVI	792	75.8	7.9	
logMAR treated eye	SVI	404	0.64	0.27	<0.001
	Non-SVI	792	0.53	0.28	
logMAR fellow eye	SVI	382	1.18	0.98	<0.001
	Non-SVI	736	0.41	0.71	

Register data showed that at 12 months from treatment start, there were only few patients (3.2%) who were eligible for but who had not been referred to low vision clinic.

At the start of treatment, the SVI-patients were significantly older compared to patients in the non-SVI-group (Student′s *t*-test for independent samples; Table 2). The SVI-patients had lower visual acuity in the treated eye at baseline. Further, patients in the SVI-group had significantly lower visual acuity in the fellow eye (Table 2).

Logistic regression analysis demonstrated an association between visual acuity in the treated eye (OR 4.066; CI_{95} 2.620–6.312) as well as between visual acuity in the fellow eye and probability for future referral to low vision clinic after initiation of treatment (OR 2.874; CI_{95} 2.418–3.416). Additionally, there was an association between age at treatment start for wet AMD and probability for referral to low vision clinic after initiation of treatment (OR 1.084; CI_{95} 1.065–1.104). With regard to duration of symptoms, crude analysis identified an association between duration of symptoms ≥4 to <6 months and referral to low vision clinic. Following adjustment for covariates, the associations between visual acuity in the treated eye, visual acuity in the fellow eye and age remained significant (Table 3).

In the SVI-group, mean visual acuity at 12 months was reduced compared to treatment start whereas in the non-SVI-group, mean visual acuity at 12 months was improved compared to baseline (Table 4). The visual acuity logMAR LOCF was significantly lower in the SVI-group compared to the non-SVI-group. The SVI-eyes had received significantly fewer intravitreal anti-VEGF-injections during the first treatment year compared to non-SVI-eyes. The total follow-up time and the total number of treatments given were similar in either group although the variation was wide.

Table 3. Risk factors for developing severe visual impairment following treatment start (Odds Ratio (OR) and 95% confidence intervals (CI_{95}). Logistic regression analysis was adjusted for visual acuity in treated eye and fellow eye, age and duration of symptoms.

		CI_{95} for OR		
	OR	Lower	Upper	p-Value
Visual acuity treated eye (logMAR)	3.161	1.896	5.271	<0.001
Visual acuity fellow eye (logMAR)	2.706	2.260	3.239	<0.001
Age	1.042	1.021	1.063	<0.001
Duration of symptoms				
0 to <2 months	0.613	0.411	0.915	0.017
≥2 to 4 months	0.596	0.400	0.889	0.011
≥4 to 6 months	1	–	–	–
≥6 months	0.619	0.400	0.959	0.032

Table 4. Visual function and number of anti-VEGF-treatments at 12 months as well as total number of anti-VEGF-treatments and total follow-up time in patients with severe visual impairment (SVI-group) compared to in patients without severe visual impairment (non-SVI-group; Student's *t*-test for unpaired data).

	Group	*N*	Mean	SD	p-Value
Change in logMAR LOCF	SVI	404	0.067	0.377	<0.001
	Non-SVI	792	−0.056	0.361	
logMAR 12 months LOCF	SVI	404	0.703	0.409	<0.001
	Non-SVI	792	0.470	0.417	
No. of injections 12 months	SVI	404	4.6	2.1	<0.001
	Non-SVI	791	5.2	2.3	
Total no. of injections	SVI	404	10.5	36.2	ns
	Non-SVI	791	10.1	26.5	
Total follow-up time (days)	SVI	402	788	611	ns
	Non-SVI	784	728	539	

LOCF = last observation carried forward.

Discussion

In the present study, both the overall incidence of severe visual impairment (SVI) and the incidence of SVI attributable to AMD declined from 2005 until 2013 in five counties in northern Sweden. Anti-VEGF treatment for wet AMD was found to stabilize visual acuity in the treated patients. Within 2 years of treatment, approximately one-third of the treated patients developed severe visual impairment (SVI) defined as visual acuity <0.3 Snellen (<20/70) and was referred to a low vision clinic for visual rehabilitation. SVI-patients were older, had lower visual acuity in the treated eye as well as in the fellow eye and had moderate long duration of symptoms of wet AMD at baseline compared to non-SVI-patients.

The observed reduction in occurrence of severe visual impairment due to AMD of 48% is well in line with previous studies from Denmark (Bloch et al. 2012) and Israel (Skaat et al. 2012). The overall occurrence of SVI was reduced to a similar extent, also in line with other studies (Skaat et al.2012). This finding is supported by official data reported from Swedish low vision clinics over the past 4 years (NYSAM 2014). The general reduction in occurrence of SVI and blindness may be attributable to improved

general and ophthalmological healthcare for cataract, glaucoma and diabetic retinopathy. The reduction in occurrence of SVI due to AMD occurs in temporal association with establishment of modern anti-VEGF-treatment for wet AMD (Rosenfeld et al. 2006; Martin et al. 2011). As SVI and blindness due to bilateral AMD is associated with substantially reduced quality of life and increased need for assistance related to daily activities (Soubrane et al. 2007), a reduction of AMD-SVI indicates important health-economic effects of treatment and strengthens the treatment indications.

One strength with measuring referral rate as a surrogate marker for SVI is the availability of large amounts of data. Referral to low vision clinic also reflects the real-life hardships for the patients and the need for visual rehabilitation measures. Limitations of the use of referral rate for occurrence of SVI are that not all patients meeting the requirements for admission to low vision clinic will be referred. Some patients may not have consulted an ophthalmologist or may not want visual rehabilitation measures. However, the study demonstrates that among patients treated for wet AMD, only few patients meeting the requirements for referral had not been admitted to a low vision clinic. It is important to point out that the eligibility criteria for referral to the regional low vision clinic have remained unchanged during the time period under study. Additionally, resources at the low vision clinics have been not been altered (NYSAM 2014). There is a possibility that following treatment for wet AMD visual acuity is improved to such an extent that the patient does no longer have SVI. This would result in an overestimation of the occurrence of SVI in the population. However, referral to low vision clinic is generally sent during follow-up at a time-point when there is some information about treatment response. Further, if a patient has been accepted at the low vision clinic for visual rehabilitation, the patient will not be declined from the low vision clinic even in case of improved visual acuity. In a recently published meta-analysis of prospective cohort studies of AMD from Europe, US and Australia (Rudnicka et al. 2015), the annual incidence of late AME in persons aged ≥50 years estimated from prevalence was 3.5/1000. The annual incidence in persons >65 years was 7.8/1000. The rate of referral to low vision clinic visual impairment in persons 65 years and older observed in the present survey was 3.1/1000 for all diagnoses and 1.9/1000 for AMD. Although the definition of severe visual impairment in our survey differs from the definition of late AMD in the large epidemiological studies included in the meta-analysis performed by Rudnicka and colleagues, the presented figures for incidence are of similar magnitude. Although the findings of the present study must be interpreted with caution, they are in line with results from large epidemiological studies. Referral to low vision clinic is considered a relevant indicator of incidence of SVI in our population.

The Swedish Macula Register provided data on treatment and treatment outcome in patients treated for wet AMD. The validation survey performed showed a low number of errors in the register. Similar extent of registration errors was found in the Swedish National Cataract Register (Håkansson et al. 2001) and data were considered reliable and useful. Extended validation survey of the SMR is ongoing nationally and further analysis is awaited before changes of the registration procedure are suggested.

Follow-up data after 12 months of treatment for wet AMD in this real-world setting showed that visual acuity was stabilized compared to visual acuity at treatment start. The effect on visual acuity was less pronounced compared to clinical trials (Rosenfeld et al. 2006; Martin et al. 2011; Heier et al. 2012). However, in other real-world cohorts, observed treatment effects are in the same range (Rung & Lövestam-Adrian 2013; Frennesson & Nilsson 2014; Borooah et al. 2015; Holz et al. 2015). In the present survey, about 12% of patients either discontinued treatment or were lost to follow-up before 12 months respectively. In a study by Hjelmqvist et al. (2011) in a clinical cohort of AMD-patients, the rate of discontinuation before 1 year was 21%. In half of the patients in the study by Hjelmqvist et al. (2011), the reasons for discontinuation were either low visual acuity or decision by treating physician. Similar findings were observed in the prospective observational study by van Asten et al. (2015). Visual acuity at the start of treatment in the present patient group was in the same range as in the clinical trials (Rosenfeld et al. 2006; Martin et al. 2011; Heier et al. 2012). However, the number of intravitreal anti-VEGF treatments given during the first treatment year was lower compared to clinical trials (Rosenfeld et al. 2006; Martin et al. 2011; Heier et al. 2012) suggesting that under-treatment may account for some of the lower treatment effect.

In the cohort of patients starting anti-VEGF treatment for wet AMD, 1/3 of patients were referred to low vision clinics during the follow-up period. The study found that patients developing SVI during treatment for wet AMD in need for vision rehabilitation measures were older, had worse visual acuity in the treated eye as well as in the fellow eye at treatment start and had moderaterly long duration of symptoms (4–6 months) compared to patients who did not develop SVI. At 12 months, the treatment outcome was significantly poorer in the SVI-patients and they had received significantly fewer anti-VEGF treatments compared to non-SVI patients. The difference in treatment outcome remained after adjustment for age and number of anti-VEGF treatments (data not shown). The prevalence of AMD increases with increasing age (Lindekleiv & Erke 2013). Further, in the Beaver Dam Eye study it has been shown that the severity of AMD in one eye largely tracks the severity in the fellow eye at all stages of the disease (Gangnon et al. 2015). The findings in the present study indicate that when a patient with reduced visual acuity in one eye due to wet AMD develops wet AMD in the fellow eye, there is an increased risk for unfavourable outcome of anti-VEGF treatment and increased risk for SVI. Short duration of symptoms at treatment start is important to obtain good visual results of anti-VEGF treatment (Rasmussen et al. 2015). It is suggested that these patients should be treated without delay and monitored with particular caution. On the other hand, very long duration of symptoms at start of treatment (>6 months) might suggest slower disease progression inducing less motivation for patients to seek ophthalmological healthcare. Our finding that long (>6 months) duration of

symptoms at treatment start is not a risk factor for worse visual outcome of anti-VEGF treatment supports this hypothesis.

In conclusion, referall rate to low vision clinic was found to be a valuable tool for estimating incidence of SVI in a population. Data from the SMR identified patients at high risk for developing SVI during anti-VEGF treatment. Further studies are of importance to evaluate measures to improve prognosis for patients at risk for SVI.

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