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Intravitreal therapy for retinal diseases in Norway 2011–2015

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ABSTRACT.

Purpose: **During the past decade, intravitreally administered biologic drugs have advanced the treatment of retinal diseases, such as wet age-related macular degeneration (AMD), diabetic macular oedema and retinal venous occlusions. The drugs as well as the necessary disease management imply considerable economic burden on healthcare systems. This Norwegian study documents the rates of use of intravitreal therapies and intercounty variation over a 5-year period.**

Methods: **We collected data from the Norwegian Patient Register for all episodes of care encompassing intravitreal therapy during the period 2011–2015. For each episode, we received information on patient age, sex, county of residence, diagnosis and name of drug injected.**

Results: **During the study period, 21 277 patients had in total 236 857 episodes of care. The number of intravitreal injections doubled from 2011 to 2015, reaching 63 601 injections in 2015, of which 77% were for diagnosed wet AMD. In 2015, the age-adjusted number of episodes varied from 19 to 55 per 1000 population aged 50+ across Norway's 19 counties. The age-adjusted number of patients treated per 1000 population aged 50+ varied from 5.22 to 8.35.**

Conclusion: **The use of intravitreal injections increased rapidly with wet AMD as the most frequent diagnosis and with varying utilization across Norway's 19 counties. The causes of the varying use of intravitreal therapies could not be established but may reflect variation in disease prevalence, treatment capacity, travel distance to the nearest ophthalmic service and lack of national treatment guidelines. The geographic variation in utilization may challenge policy goals of equitable care and warrants further studies.**

Key words: EGFR – intravitreal injection – retinal disease – statistics – wet age-related macular degeneration

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Background

Vascular endothelial growth factor (VEGF) represents a family of signal proteins that stimulate angiogenesis. Vascular endothelial growth factor (VEGF) plays an important role in several disease processes, and the ability to inhibit these signal proteins with biologic pharmaceuticals offers treatment potentials for malignancies and retinal disease. Among the latter, VEGF inhibitors were first adopted for neovascular age-related macular degeneration (wet AMD), which affects approximately 2.5% of the elderly in Norway (Erke et al. 2012). Vascular endothelial growth factor (VEGF) inhibitors are also increasingly used for other common retinal diseases such as macular oedema caused by retinal vein occlusion, diabetes and myopic neovascular membranes.

Vascular endothelial growth factor (VEGF) inhibitors have had considerable impact on the practice of ophthalmology over the last decade. Given the previous lack of effective treatment for wet AMD, VEGF inhibitors represent a paradigm shift for this patient group. The drugs improve vision prognosis, but the chronic nature of the relevant retinal diseases implies a need for intravitreal injections, at 4–12 weeks intervals, potentially for many years. The mode of administration is challenging because the drugs are injected directly into the vitreous body, requiring sterile procedures. Consequently, the drugs themselves as well as the medical management consume considerable resources.

Currently, there are two VEGF inhibitors approved for ophthalmic treatment in Norway. Ranibizumab (Lucentis; Novartis, Basel, Switzerland) is a VEGF antibody fragment while aflibercept (Eylea; Bayer Health Care, Leverkusen, Germany) is a recombinant protein with higher VEGF affinity than

the natural VEGF receptors. Both drugs have market approval for wet AMD (Brown et al. 2006; Rosenfeld et al. 2006; Heier et al. 2012), macular oedema secondary to retinal vein occlusions (Brown et al. 2010; Campochiaro et al. 2010; Heier et al. 2014; Korobelnik et al. 2014a,b; Campochiaro et al. 2015), diabetic retinopathy (Nguyen et al. 2012; Korobelnik et al. 2014a,b) and myopic neovascular membranes (Wolf et al. 2014; Ikuno et al. 2015). Additionally, bevacizumab (Avastin; Roche, Basel, Switzerland) is used 'off-label' for the same diseases. Bevacizumab is a VEGF antibody approved for several malignancies but has also been tested in several studies for retinal disease (CATT Research Group et al. 2011; Chakravarthy et al. 2013; Diabetic Retinopathy Clinical Research Network et al. 2015; Berg et al. 2016; Scott et al. 2017). Finally, a dexamethasone implant (Ozurdex; Allergan, Dublin, Ireland) is approved for the treatment of macular oedema secondary to vein occlusions and diabetes.

Aflibercept was approved for AMD in December 2012 and then later for central vein occlusion (September 2013), diabetic macular oedema (August 2014), branch retinal vein occlusion (February 2015) and myopic choroidal neovascularization (November 2015). Ranibizumab was approved for treatment of AMD in 2007. In 2015, the price of Lucentis® and Eylea® were €794 and €815, respectively, while the price of an Avastin® vial was €344. Throughout the study period, Lucentis® and Eylea® vials usually were split into at least two syringes, while Avastin® vials were split into multiple syringes.

Norway has a public, tax-financed healthcare system with a maximum patient co-payment of €240 per year (2019) for drugs, physician visits and hospital care altogether. A very few patients receive treatment for retinal disease from private providers. An overarching goal of the system is general access to care irrespective of age, sex, income and county of residence.

The aim of this study was to describe the use of intravitreal therapies in Norway during a 5-year period. We examined the following research questions:

1. How many patients received intravitreal injections during the period 2011–2015?
2. What were their diagnoses?
3. Which drugs were used?
4. Was there geographic variation in the utilization of the therapies?

Methods and Material

We received data from the Norwegian Patient Register for all somatic hospitals for the period 2011–2015. The observation unit was episode of care (outpatient clinic visit, day care, in-hospital care). The inclusion criteria were as follows:

1. NOMESCO classification of surgical procedures (NCSP) code CKD05 (intravitreal injection).
2. Special code S011LA01 (verteporfin treatment).
3. NCSP code CKC12 (transpupillary laser treatment).
4. NCSP code ZXC15 (photodynamic technique).

For each episode, we received information on the following variables:

1. Year and date of episode.
2. Type of episode (outpatient clinic visit, day care, in-hospital care).
3. Anonymous patient ID number.
4. Patient sex.
5. Patient age (10-year groups).
6. Patient's county of residence (19 different).
7. Diagnosis related groups number and cost weight.
8. ICD-10 main diagnosis.
9. ICD-10 supplementary code if it were as follows:

   i. H35.3 (degeneration of macula or the posterior pole).
   ii. H34.8 (other specified retinal vessel occlusions).
   iii. H36.0 (diabetic retinopathy).
   iv. E10-14 (diabetes).

Procedure code for pharmaceuticals:

   v. Medical procedure (Norwegian classification of medical procedures) code 1–20.
   vi. NCSP code 1–20.

Dummies for the following codes:

   vii. NCSP code CKD05 (intravitreal injection).
   viii. NCSP code S01LA01 (treatment with verteporfin).
   ix. NCSP code CKC12 (transpupillary laser treatment).
   x. NCSP code ZXC15 (photodynamic technique).

We described the data with simple descriptive methods (frequencies, means, etc.). Because the data captured the total use of intravitreal treatment and not a sample, there was no sample uncertainty involved, and significance tests were not relevant. County-wise variations were explored by age-adjusted rates (per 1000 population). For each county, we first estimated the rates in each 10-year age group. Subsequently, we estimated each county's total rate as if it had the same age distribution as the entire country. Data were analysed in Stata® version 14 (StataCorp LLC, College Station, TX, USA).

Results

The data set

The entire data set encompassed 295 035 episodes of care among 43 383 patients during the period 2011–2015. With photodynamic treatment as inclusion criterion, we captured episodes for nonophthalmic diagnoses such as actinic keratosis. These episodes were removed along with episodes with photodynamic and laser treatment, which were not the topic for this study. The remaining data set now encompassed 236 857 episodes with intravitreal treatment (Table 1).

In 2015, 56% of the patients were women and 70% were aged 70+ (Table 2). Nearly all of the episodes (99.1%) were outpatient clinic visits. In the following, we collapse inpatient care, day treatment and outpatient treatment and use the term episode of care for all three.

Diagnoses

The most frequent diagnoses among the patients were H35.3 (degeneration of the posterior pole including wet AMD; 81% in 2011 and 76% in 2015), H34.8 (other retinal vessel occlusions; 8% in 2011 and 13% in 2015) and H36.0 (diabetic retinopathy; 5% in 2011 and 8% in 2015). (Table 1).

Geographic variation

The age-adjusted rate of intravitreal treatment in 2015 varied from 19 per 1000 population aged 50+ (Hedmark county) to 55 (Troms county; mean 26.02; Table 3; Fig. 1). The same counties also had, respectively, the lowest and the highest rates in 2011. In 2015,

Table 1. Number of episodes of care with intravitreal injection with an ophthalmic diagnosis as main or supplementary diagnosis, according to year and diagnosis.

	2011	2012	2013	2014	2015	2011,%	2015, %	Growth (2011–2015)
Wet AMD (H35.3)	25 254	30 524	37 679	43 530	48 415	81%	76%	92%
Diabetic retinopathy (H36.0)	1616	2279	2762	4070	4893	5%	8%	203%
Retinal detachment with tear (H33.0)*	107	158	147	158	151	0%	0%	41%
Retinal tear without detachment (H33.3)*	11	26	36	38	21	0%	0%	91%
Background retinopathy and retinal vascular changes (H35.0)	294	499	340	157	203	1%	0%	-31%
Retinal vein occlusion (H34.8)	2483	3644	4588	7052	8524	8%	13%	243%
Other eye disease (ICD10 H-code)	1297	1443	1455	1609	1394	4%	2%	7%
Total	31 062	38 573	47 007	56 614	63 601	100%	100%	105%

* These episodes may represent miscoding or treatment for wet age-related macular degeneration (AMD) in patients with retinal detachment or tear.

Table 2. Number of patients with eye-related diagnoses and intravitreal injection therapy in 2015, according to age and sex.

	Female		Male		Total	
Age group (years)	*N*	Per cent of total patients (%)	*N*	Per cent of total patients (%)	*N*	Reverse cumulative distribution (%)
0–10	4	36	7	0	11	100
11–20	6	33	12	0	18	100
21–30	40	48	44	0	84	100
31–40	51	37	88	1	139	99
41–50	122	37	207	2	329	98
51–60	329	40	495	4	824	95
61–70	1014	47	1150	10	2164	88
71–80	1905	55	1551	13	3456	70
81–90	2562	65	1379	12	3941	41
90+	651	73	241	2	892	8
Total	6684	56	5174	44	11 858	–

Table 3. Age-adjusted* number of episodes of care with intravitreal injection (per 1000 population aged 50+) for patients aged 50+, according to county and year.

	2011	2012	2013	2014	2015
Akershus	26.16	30.75	36.54	39.36	41.80
Aust-Agder	18.99	21.75	27.59	27.11	25.94
Buskerud	14.02	17.12	23.12	32.57	38.99
Finnmark	20.45	28.90	35.58	39.21	37.90
Hedmark	8.30	9.97	15.12	19.90	18.57
Hordaland	9.85	14.22	19.69	25.19	26.47
Møre og Romsdal	12.19	16.17	21.25	28.60	33.53
Nord-Trøndelag	12.50	15.92	21.21	24.05	26.47
Nordland	18.24	22.37	23.59	27.33	28.89
Oppland	14.86	15.01	15.37	25.38	20.70
Oslo	24.79	31.94	36.73	40.71	44.80
Rogaland	26.40	29.42	32.72	33.78	38.19
Sogn og Fjordane	11.25	11.02	12.29	15.97	21.39
Sør-Trøndelag	18.81	22.10	26.90	33.72	36.47
Telemark	10.29	11.30	13.83	19.58	30.92
Troms	29.11	36.82	41.26	45.89	55.40
Vest-Agder	12.38	15.31	18.40	21.30	26.02
Vestfold	22.89	29.63	36.76	41.06	42.57
Østfold	20.21	24.52	28.59	36.34	39.62

* Injections without information on county were omitted from analysis.

the age-adjusted number of patients per 1000 population aged 50+ varied from 5.22 in Hordaland county to 8.35 in Troms county (mean 6.23; Table 4; Fig. 2).

Drug variation

For some of the CKD05 procedures (injection of pharmaceutical in the vitreous body), none of the four mentioned drugs were registered (4%), while for some episodes more than one of the mentioned drugs were registered (2%; Table 5). In addition, 2% of episodes were included in a randomized multicenter study of ranibizumab and bevacizumab for which the drug used was not registered in the data. These episodes were excluded from the numbers presented per drug. Notably, ranibizumab and bevacizumab were in use for the entire study period 2011–2015, while aflibercept was available from 2013.

The number of episodes with bevacizumab increased from 18 171 in 2011 to 27 701 in 2015 (52% increase), while it declined from 9026 to 4348 for ranibizumab (52% decrease; Table 5). Use of aflibercept was reported for 3162 episodes in 2013 and 27 938 in 2015. Market share in terms of episodes in 2015 was 44% for aflibercept, 44% for bevacizumab, 7% for ranibizumab and 2% for dexamethasone.

In 2015, aflibercept was used somewhat more for H35.3 (degeneration of macula and posterior pole) and H36.0 (diabetic retinopathy) than bevacizumab, while the opposite was the case for retinal vein occlusions (Table 6).

There was considerable variation across the counties in terms of choice of pharmaceuticals (Table 7). In 2015, there were no episodes of care with bevacizumab in Aust-Agder county, while this county had the highest rate for ranibizumab. All other counties had a mix of aflibercept and bevacizumab, but with variation in the distribution of the two drugs.

Discussion

The present study is the first of its kind in Norway. Capturing intravitreal

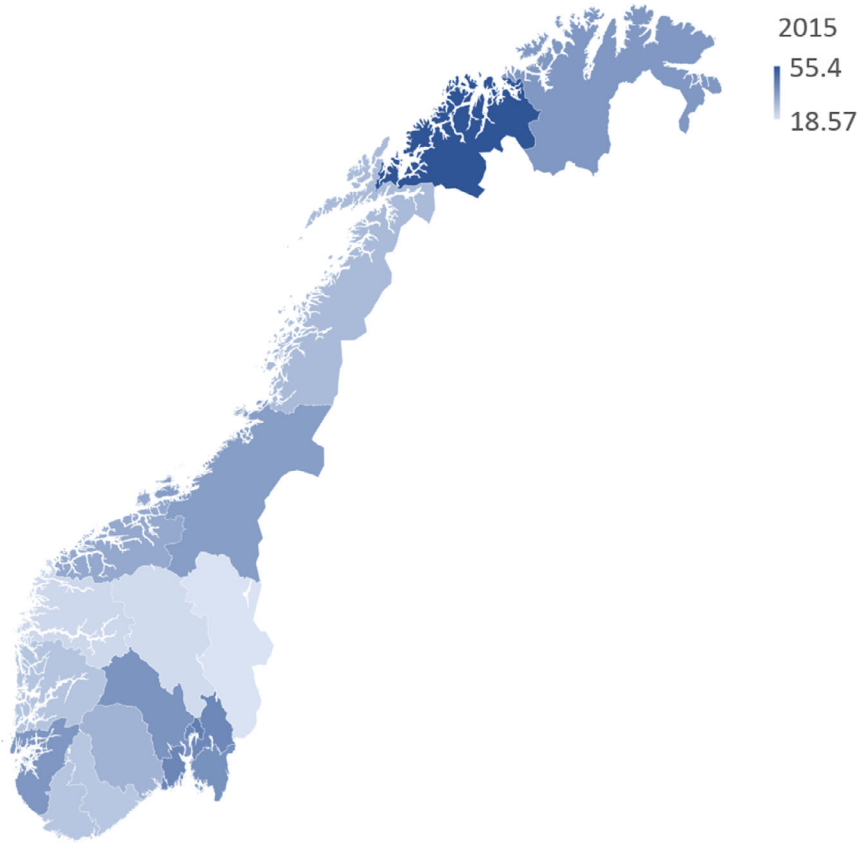

Fig. 1. Age-adjusted number of episodes of care with intravitreal injections for patients aged 50+, according to county (per 1000 population 50+).

Table 4. Age-adjusted number of patients who received intravitreal injection according to county and year (number of patients per 1000 population aged 50+).

	2011	2012	2013	2014	2015
Akershus	4.17	5.13	5.71	6.17	6.53
Aust-Agder	3.91	4.67	5.14	5.48	5.04
Buskerud	2.88	3.24	4.32	5.56	6.76
Finnmark	3.75	5.55	5.69	5.95	5.53
Hedmark	3.11	3.68	4.76	5.01	5.25
Hordaland	2.78	3.53	4.34	5.31	5.22
Møre and Romsdal	3.35	4.34	4.68	5.76	6.51
Nord-Trøndelag	4.06	4.97	5.28	5.62	6.20
Nordland	3.90	4.62	5.17	5.79	6.29
Oppland	3.79	4.06	4.54	5.78	5.72
Oslo	4.11	5.23	5.76	6.52	6.99
Rogaland	5.10	5.50	6.07	6.34	7.02
Sogn and Fjordane	3.15	3.44	4.31	4.81	5.28
Sør-Trøndelag	4.18	5.13	5.77	6.42	6.82
Telemark	2.89	3.27	4.12	4.60	5.38
Troms	4.92	6.11	6.48	7.14	8.35
Vest-Agder	3.38	3.21	4.19	4.42	5.03
Vestfold	4.06	5.50	6.20	7.19	7.51
Østfold	3.67	4.48	5.34	6.15	6.98

procedures for an entire country during a 5-year period, this study documents a considerable increase in the use of intravitreal procedures as well as geographic variation in utilization and choice of drug.

The results of this study illustrate the impact VEGF inhibitors have had on ophthalmic practice during the last decade. In 2015, approximately 60 000 intravitreal procedures were performed while this type of treatment did not exist 10 years earlier. For the largest patient group (wet AMD), no effective therapy was available until intravitreal therapy was introduced. The age-adjusted prevalence of wet AMD can hardly have changed much during a decade, and there are good reasons to believe that the new treatment modality explains the rapid growth. For all patient groups, intravitreal treatment offers the prospect of maintaining visual activities of daily living. However, intravitreal treatment also presents challenges for ophthalmic clinics and healthcare systems. These challenges are not unique to Norway but are also observed in the United Kingdom, the United States and probably all industrialized countries (Keenan et al. 2012; Erie et al. 2016).

Across counties, we observe considerable variation in the rate of intravitreal injections and population proportions receiving such therapy. The variation may have several explanations. First, there may be differences in the prevalence of retinal diseases, foremost wet AMD. Considerable variation in AMD prevalence has been reported across countries and ethnic groups (Wong et al. 2014; Pennington & DeAngelis 2016; Colijn et al. 2017; Jonas et al. 2017; Mitchell et al. 2018). Unfortunately, no studies of regional variation have been undertaken in Norway. To the extent cardiovascular disease (CVD) and diabetes are associated with anti-VEGF-treated retinal diseases, we found no association between rates of intravitreal therapy and CVD or diabetes mortality (https://www.fhi.no/hn/helseregistre-og-registre/dodsarsaksregisteret/). Second, variation in treatment capacity necessarily translates into variation in utilization. Surprisingly, no reliable data on treatment capacity or ophthalmologist density are available for Norway. Finally, travel distances to retina services may influence utilization of intravitreal therapy. However, the Norwegian Patient Register could not provide such data.

We do not have information on budget changes in the ophthalmic departments. Nevertheless, there is an impression among Norwegian ophthalmologists that capacity varies across counties and work pressure has increased considerably as a consequence of the emergence of anti-VEGF therapy. Inevitably, the present-day situation represents a risk in terms of

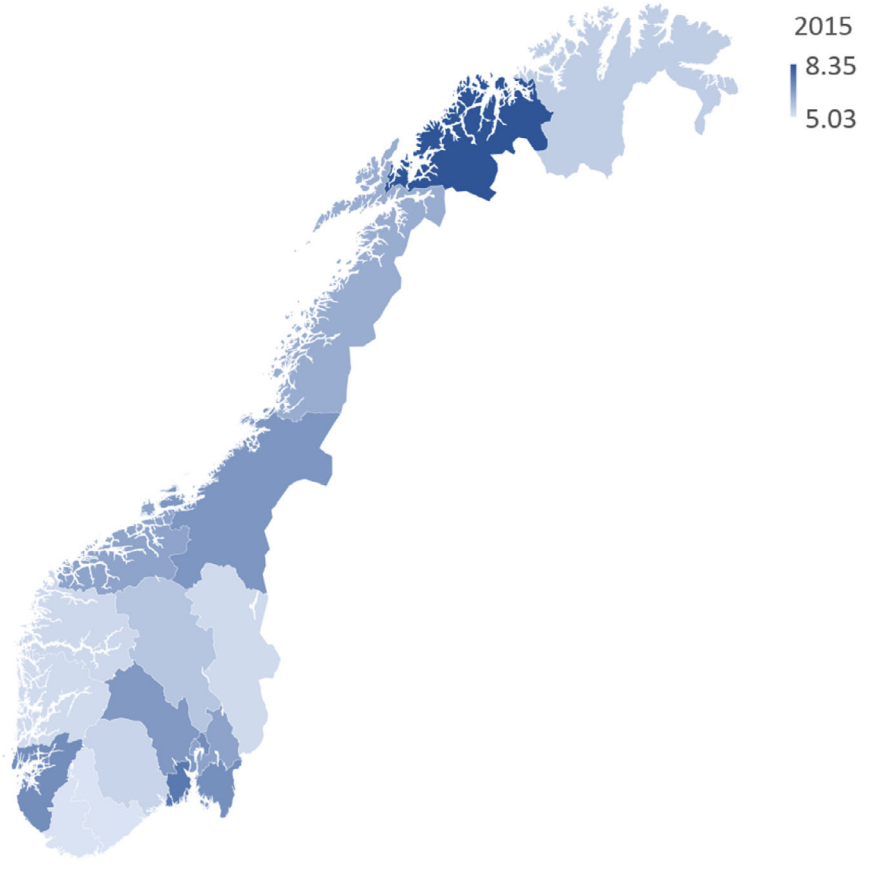

Fig. 2. Age-adjusted number of patients aged 50+ who received intravitreal injections, according to county (per 1000 population aged 50+).

Table 5. Number of episodes of care with intravitreal injection registered with an eye diagnosis as main or supplementary diagnosis, according to year and drug.

		2011	2012	2013	2014	2015	Growth 2011–2015	Total of 2011–2015
Aflibercept	*N*	0	0	3162	17 798	27 938	27 938	48 898
	%			7	31	44	Undefined	21
Bevacizumab	*N*	18 171	26 994	30 411	26 937	27 701	9530	130 214
	%	58	70	65	48	44	52	55
Dexamethasone	*N*	0	0	735	855	1045	1045	2635
	%			2	2	2	Undefined	1
LUCAS study*	*N*	2159	1801	926	121	0	−2159	5007
	%	7	5	2	0	0	−100	2
Ranibizumab	*N*	9026	7260	9027	7331	4348	−4678	36 992
	%	29	19	19	13	7	−52	16
Two or more drugs	*N*	55	151	377	896	1074	1019	2553
	%	0	0	1	2	2	1853	1
Unknown	*N*	1651	2367	2369	2676	1495	156	10 558
	%	5	6	5	5	2	−9	4
Total	*N*	31 062	38 573	47 007	56 614	63 601	32 539	236 857
	%	100	100	100	100	100	105	100

* The LUCAS study was a randomized controlled trial of bevacizumab and ranibizumab. Injections in this study had a special treatment code.

with university eye clinics (Akershus, Hordaland, Oslo, Sør-Trøndelag and Troms) is towards a steady increase in activity. It seems self-contradictory that the need for intravitreal treatment regionally would reach a plateau. Rather, we believe the finding indicates a recession. The Norwegian Ophthalmologic Society, among others, has long expressed concern that training and education of new ophthalmologists do not meet the growing demand, and it is well known that Norwegian rural areas in particular have major problems recruiting retina specialists. The data raise concerns about undertreatment in some counties. If this were the case, it would be in conflict with overarching principles of the Norwegian healthcare system. The aim is to offer all individuals the necessary medical treatment irrespective of age, sex, income or place of residence (19).

An additional explanation of regional variation may be lack of regional or national treatment guidelines for retinal diseases, both regarding drug of choice and treatment protocol. Moreover, Norway is without national quality registers resembling the Swedish macula register ("Svenska makulareg-

undertreatment with loss of vision as a consequence. We lack solid data but suggest that varying budgets and capacities, in addition to variation in thresholds for initiating or discontinuing therapy, are probable explanations of the differing injection rates. Notably, the rate of injections halts or decreases over time in a few relatively rural counties (Aust-Agder, Finnmark, Hedmark and Oppland). By contrast, the general trend of more urban counties istret") (Westborg et al. 2017). The aim of this register is that the treatment of wet AMD shall have good quality for all Swedish patients. In contrast to the register data used in this study, the Swedish macula register captures visual

Table 6. Number of episodes of care with intravitreal injection in 2015, according to diagnosis and drug.

	Aflibercept	Bevacizumab	Dexamethasone	Ranibizumab	Two or more drugs	Total
Degeneration of macula and posterior pole (H35.3)	22 019	21 255	395	3082	846	47 597
Diabetic retinopathy (H36.0)	2066	1779	177	547	190	4759
Retinal detachment (H33.0)	4	21	2	0	0	27
Retinal rift (H33.3)	7	4	0	1	0	12
Background retinopathy and retinal vascular changes (H35.0)	77	85	2	27	6	197
Retinal vein occlusion (H34.8)	3364	4092	302	620	29	8407
Other eye disease (ICD10 H-code)	401	465	167	71	3	1107
Total	27 938	27 701	1045	4348	1074	62 106

Some episodes with procedure code CKD05 (injection of drug in vitreous body) did not have name of drug registered. These episodes were omitted from this table.

Table 7. Age-adjusted rate of intravitreal injections* (per 1000 population aged 50 +) according to county and drug.

County	Aflibercept	Bevacizumab	Dexamethasone	Ranibizumab	Two or more drugs	Total
Akershus	17.95	19.59	0.48	2.17	0.93	41.11
Aust-Agder	15.31	0.00	0.56	9.58	0.40	25.84
Buskerud	23.43	12.86	0.84	0.86	0.19	38.18
Finnmark	18.11	18.24	0.00	0.82	3.62	40.79
Hedmark	9.44	6.39	1.00	0.39	0.73	17.95
Hordaland	5.65	19.11	0.28	0.01	0.39	25.45
Møre and Romsdal	13.41	17.50	0.41	1.23	0.10	32.64
Nord-Trøndelag	12.08	10.98	0.49	2.03	0.50	26.08
Nordland	16.47	3.15	0.44	7.62	0.06	27.73
Oppland	15.65	4.10	0.07	0.58	2.09	22.49
Oslo	17.78	21.31	0.43	3.50	0.28	43.31
Rogaland	15.13	19.42	1.79	0.22	0.04	36.59
Sogn and Fjordane	4.67	14.28	0.63	0.14	0.85	20.57
Sør-Trøndelag	12.44	18.90	0.39	3.88	1.54	37.16
Telemark	13.88	16.48	0.07	0.06	0.03	30.52
Troms	22.28	27.99	0.09	2.11	1.31	53.78
Vest-Agder	14.89	1.77	0.50	7.77	0.94	25.87
Vestfold	21.88	11.88	0.90	6.24	11.12	52.03
Østfold	20.32	17.27	0.15	0.28	6.98	45.00

* Episodes of care with the procedure code CKD05 (injection vitreous body) but without information on type of drug were omitted from analysis. Injection rates are therefore reduced accordingly.

acuity and consequently the ability to study treatment effectiveness. As treatment of retinal disease poses a major challenge to modern ophthalmic care, we believe clinical quality registries should always be implemented as an aid to medical practice and health governance.

A crucial issue is the future number of intravitreal injections. In 2015, 9027 patients received intravitreal therapy for wet AMD [76% of 11 858 = 9027 (Table 2)]. Statistics Norway predicts that the number of individuals aged 65+ will be 1 063 000 in 2025, that is 10 years after the end of the present study. Assuming that 2.5% of individuals aged 65+ will be candidates for wet AMD treatment (Erke et al. 2012); it would represent a total of 26 600 individuals. In other words, by comparison with 2015, ophthalmic services will need to triple their capacity to treat all individuals with wet AMD in 2025. In addition, many patients will need intravitreal therapy for other eye diseases, not least diabetic retinopathy.

A strength of this study lies in the use of a national, public patient register in a country where a few patients receive treatment outside the public healthcare system. Weaknesses lie in the lack of prevalence data and incomplete coding by some ophthalmic centres. In total, 6% of episodes of care did not have information on the drug used, and 4% lacked a code for uni- versus bilateral treatment. While some ophthalmologists treat both eyes on the same day, others choose to have a few days between the two injections. Lack of information on uni- versus bilateral treatment may explain some of the geographic variation in the number of therapies per population, but not the number of patients per population. A minority of the episodes were related to additional surgical diagnoses such as H33.0 or H33.3 (retinal tears with or without detachment). Indeed, intravitreal injection of pharmaceuticals may be part of vitreoretinal surgical treatment, but the diagnoses may also represent erroneous coding. In Norway, the ICD10 code H35.3 (degeneration of macula and the posterior pole) includes both wet AMD and several other retinal diseases that may be treated with VEGF inhibitors. Although wet AMD undoubtedly is the prevailing H35.3

diagnosis, the proportions of other H35.3 diagnoses remain unknown.

Conclusion

The number of intravitreal injections doubled from approximately 31 000 episodes in 2011 to 64 000 in 2015 with wet AMD as the most frequent diagnosis. Across counties, there was considerable variation in the use of intravitreal injections as well as the choice of drug. These variations may challenge the well-established Norwegian policy of equitable care and warrant further studies.

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