Real world evidence of use of anti-VEGF therapy in Denmark

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ABSTRACT
Objective: This study evaluates real-world evidence regarding the frequency of anti-vascular-endothelial-growth-factor (VEGF) injections during the first year of treatment of naïve patients with neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME) and retinal vein occlusion (RVO) from the Danish National Patient Registry. There was a switch in anti-VEGF treatment for naïve nAMD patients during the study period, following the introduction of aflibercept, which was expected to reduce the injection frequency relative to ranibizumab due to a perception of prolonged treatment duration of aflibercept.

Methods: All treatment-naïve nAMD, DME or RVO patients who received an intravitreal injection in Denmark from 1 January 2012 to 31 July 2015 were eligible for inclusion. Patients were required to have been treated for at least one year and, for nAMD, to have received at least three injections during the first four months of treatment. Patients were allocated to half-year groupings (2012/1 to 2014/1) based on registration of their first intravitreal injection. Injection frequency during the first year of treatment was calculated for each group and t-tests investigated whether injection frequencies changed over time.

Results: In treatment naïve nAMD patients (n = 500), the mean (SD) number of anti-VEGF injections increased significantly from 6.04 (1.71) in 2012/1 to 6.73 (1.62) in 2014/1 (p = .001; 2012/1 and 2012/2 vs. 2014/1) across all treatments. A similar trend was found for DME patients (n = 76) from 2012/1 to 2014/1 and RVO patients (n = 82) from 2012/2 to 2014/1, with mean injection frequencies increasing significantly from 5.14 (2.29) to 5.93 (1.98) (p = .007), and from 4.83 (1.21) to 6.08 (1.55) (p = .024), respectively. Post hoc sensitivity analysis also found a significant increase in injection frequency in nAMD patients who did not receive a loading phase (4.55 in 2012/1 and 5.05 in 2014/1; p = .006; n = 616).

Conclusions: In contrast to the decrease in injection frequency predicted with a switch to aflibercept treatment for nAMD, our study showed that injection frequencies increased significantly from 2012 to 2014 in patients initiating therapy across the three diseases. 

Introduction

Several randomized controlled studies have shown the beneficial effects of anti-vascular-endothelial-growth-factor (VEGF) therapy in the treatment of neovascular age-related macular degeneration (nAMD)1–6, diabetic macular edema (DME)7–10 and retinal vein occlusion (RVO)11–16. Patients with nAMD, DME or RVO, regardless of diagnosis, are routinely treated with one of the two approved anti-VEGF therapies: ranibizumab (Lucentis®) or aflibercept (Eylea®). The anti-VEGF therapy bevacizumab (Avastin®) is also used off label for the treatment of retinal disease, and was reported in a 2014 survey by the American Society of Retinal Specialists as the treatment of first choice in the US, while in the same survey ranibizumab was identified as the first line therapy in the EU17. In particular, bevacizumab is not recommended for use in treatment of eye diseases in the national Danish treatment guidelines18–20 and is therefore very rarely used in treatment of nAMD, DME or RVO in Denmark.

Clinical practice for treatment with ranibizumab in nAMD was originally informed by the MARINA1 and ANCHOR6 randomized phase 3 studies, where patients received fixed monthly injections. Although a fixed monthly treatment regimen for ranibizumab optimizes the functional results, patient burden, logistical and economic issues have made this regimen difficult to adhere to. Subsequent studies, such as CATT and PrONTO, have shown that gains in visual acuity (VA) can be maintained when following a pro re nata (PRN) regimen, where patients are treated as needed based on monthly optical coherence tomography (OCT) evaluation21,22. The initial European label for ranibizumab was for visual acuity guided PRN dosing with monthly monitoring following three monthly loading doses23. Hence, treatment in routine clinical practice is associated with less-than-monthly...
Materials and methods

Registry selection

This study is a non-interventional, retrospective study using secondary data from the Danish National Patient Registry and the Civil Registration System (Det Centrale Personregister, CPR-registret). These registries cover the total Danish population. The study was approved by and data were obtained from the Danish Health and Medicines Data Authority (Statens Serum Institut, project ID: FSEID-00001379). The data type is delivered on a patient level where each patient is uniquely identified in the registry data but the delivered data is anonymized. No patient characteristics were extracted from the registries. Informed consent was not required due to the retrospective design of the study. Extracted data covers only anti-VEGF injections and not outcomes. As such, the study did not identify any new safety signals.

Inclusion criteria

Patients were included in the study if, in the period from 1 January 2012 until 31 July 2015, they registered with at least one procedure code for an intravitreal injection (codes KCKD05 and KCKD05B), had a diagnosis of nAMD (based on treatment codes DH353J, DH353K), DME (DH360K) or RVO (DH348C, DH348D, DH348E), were treatment-naïve to anti-VEGF, received treatment during their first year of treatment, had at least one year of follow-up, and had at least one injection after the first year of treatment. Figure 1 describes the patient selection process in our study.

In addition, for the nAMD patient group, patients were required to have a loading phase of at least three injections during the first four months of treatment. The requirement of a loading phase is consistent with another observational study using data from one treatment center in Denmark and reflects the national treatment guidelines for initiating treatment in treatment-naïve patients. However, a large proportion of patients did not receive a loading phase, thus a post hoc sensitivity analysis on patients who did not receive a loading dose and on all nAMD patients with at least one year of treatment was performed.

Study design

Patients in each diagnostic group (nAMD, DME or RVO) were allocated to a half-year grouping, based on the month when the first intravitreal injection was registered. There were five half-year groupings for each indication from 2012/1 to 2014/1. The final half year grouping was 2014/1 to allow for one complete year of follow-up. As individual patients were...
normality. The standard Shapiro–Wilk test was used to test data for normal distribution. If data were not normally distributed (at significance level of 0.05), data were log-transformed and ANOVA was repeated. If these data were also not normally distributed, then the non-parametric Kruskal–Wallis one-way analysis of variance was performed as a robustness check.

If the null hypothesis is rejected in the ANOVA test, then the data do not support that the mean injection frequency is the same throughout the study period. To identify periods between which there were differences in the injection frequency, multiple t-tests with Bonferroni correction were performed.

A Welch two-sample t-test was also performed utilizing data from patients initiated in 2012 versus patients initiated in the first half-year of 2014. Since Welch’s t-test does not require equal variance in the two populations, it is preferred to a Student’s t-test. The t-test is based on an assumption of normality, but is relatively robust to violations of this assumption. However, the Mann Whitney U test was performed as a robustness check in case of non-normality of distribution as indicated by Shapiro–Wilk.

### Results

#### Patient selection

A large number of patients (n = 19,522) with intravitreal injections between 1 January 2012 and 31 July 2015 were identified (Figure 1). A significant number of these patients were classified as “Other” (n = 8919), having been registered for intravitreal injections with indications other than nAMD, DME or RVO, and were excluded from the analysis. Among the three indications included in our study, most patients were treated for nAMD (n = 7776), followed by RVO (n = 1610) and DME (n = 1217). Non-naïve patients who initiated treatment prior to 1 January 2012 (n = 7568) were excluded. Patients with less than one year of follow up (n = 1049) or less than one year of treatment (n = 712) were also excluded. Finally, nAMD patients who did not receive a loading phase (n = 616) were excluded from the main analysis but included in the post hoc sensitivity analysis. In total, 1274 patients were included in our analysis (nAMD, n = 500 in the main analysis and n = 1116 in the sensitivity analysis; DME, n = 76 and RVO, n = 82).

#### Frequency of injections

##### nAMD patients

The year 1 mean number of anti-VEGF injections of treatment-naïve patients can be found in Table 1(a) (Figure 2(a)). The mean number of anti-VEGF injections for patients who received a loading phase (n = 500) increased during the study period, from 6.04 in the first half-year of 2012 to 6.73 in the first half-year of 2014. ANOVA showed that the injection frequency changed over time (p = .035). As the Shapiro–Wilk test showed the data to be non-normal (p < .05 for all six-month periods), data were log-transformed but still not normally distributed (p < .05 for all periods).

The Kruskal–Wallis had a p-value of .078. The multiple t-tests with Bonferroni corrections identified one pairwise
comparison that was significantly different (2012/1 versus 2014/1, \( p = .031 \)). Finally, the Welch two-sample \( t \)-test, which evaluated 2012/1 and 2012/2 jointly versus 2014/1 (6.08 vs. 6.73, respectively), found the mean number of injections in 2014/1 was higher than the mean in 2012 (\( p = .001 \)). A Mann Whitney \( U \) test was used as a robustness check due to non-normality and gave the same conclusion (\( p = .004 \)).

The sensitivity analysis for all patients receiving treatment for at least one year, but who did not receive a loading phase (\( n = 616 \)), showed a qualitatively similar trend, where the injection frequency increased from 4.55 in 2012/1 to 5.05 in 2014/1 (Table 1(a)). ANOVA had a \( p \)-value of .002 and the Welch two-sample \( t \)-test a \( p \)-value of .006. Additional test statistics are available in the online supplementary material.

The injection frequency for all nAMD patients, irrespective of whether or not they received a loading phase (\( n = 1116 \)), was stable throughout the study period with a mean of 5.49 in 2012/1 and a mean of 5.71 in 2014/1. The ANOVA test failed to reject the null hypothesis of the injection frequency being similar across time periods (\( p = .118 \)) for this population. Hence, the overall injection frequency is stable despite an increasing trend in injection frequencies in both patient cohorts with and without a loading phase. This may be explained by patients who do not receive a loading phase receiving fewer injections and the weight of this population in the weighted average increases as the proportion of patients who do not receive a loading phase increases during the study period, from 37% in 2012/1 to 61% in 2014/1. Additional statistical data are provided in the online supplementary material.

**DME and RVO patients**

Injection frequency was also evaluated in treatment-naive DME patients (\( n = 76 \)) and RVO patients (\( n = 82 \)) even if there was no switch in treatment for these diseases during the study period. The mean (standard deviation) number of injections can be found in Table 1(b) (Figure 2(c) and (d)). Statistical analysis was not possible in the 2012/1 half-year patient grouping for RVO patients, as only one patient was eligible for inclusion.

For some time periods assessed, low patient numbers reduced the robustness of the analyses. However, the general trend in injection frequency during the study period was similar to that observed for nAMD patients. For DME patients, the mean injection frequency increased from 5.14 in 2012/2 to 5.93 in 2014/1, while the corresponding numbers for RVO patients were 4.83 in 2012/2 and 6.08 in 2014/1. Further statistical data are provided in the online supplementary material.

For both DME and RVO, the Shapiro–Wilk test did not reject the assumption of normality for any period (\( p > .05 \) for all periods). In DME patients, ANOVA testing found no statistically significant differences between the half-year groups (\( p = .090 \)). The Welch two sample \( t \)-test found the mean number of injections in 2014/1 to be higher than in 2012 (\( p = .007 \)).

In RVO patients, ANOVA testing found there to be a difference between at least two half-year groups (\( p = .002 \)). Multiple \( t \)-tests with Bonferroni correction showed a significant difference between 2013/1 and 2013/2, as well as between 2013/1 and 2014/1. The Welch two sample \( t \)-test found that the mean number of injections in 2014/1 was higher than the mean in 2012/2 (\( p = .024 \)).

**Discussion**

This study retrospectively evaluated data from the Danish National Patient Registry, which contains data from all Danish treatment centers. The objective was to obtain insight into real-world treatment patterns of anti-VEGF therapies, in particular, the development in injection frequency over time in treatment-naive nAMD, DME and RVO patients.

Data were captured from the time period of 2012 to 2014, when there was a known switch in Denmark from

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**Table 1. Frequency of anti-VEGF injections in year 1 of treatment in treatment-naïve patients.**

| Grouping year/half year | nAMD with loading (\( n = 500 \)) | nAMD without loading (\( n = 616 \)) | All nAMD (\( n = 1116 \)) |
|------------------------|-----------------------------------|-------------------------------------|--------------------------|
|                        | Mean (SD)                         | Mean (SD)                           | Mean (SD)                |
| 2012/1                 | 6.04 (1.71)                       | 4.55 (1.92)                         | 5.49 (1.93)              |
| 2012/2                 | 6.17 (1.65)                       | 3.75 (1.74)                         | 5.76 (1.90)              |
| 2013/1                 | 6.10 (2.06)                       | 5.24 (1.53)                         | 6.36 (1.84)              |
| 2013/2                 | 6.40 (1.64)                       | 4.91 (1.32)                         | 5.38 (1.59)              |
| 2014/1                 | 6.73 (1.62)                       | 5.05 (1.55)                         | 5.71 (1.78)              |

**b. DME and RVO patients.**

| Grouping year/half year | DME (\( n = 76 \)) | RVO (\( n = 82 \)) |
|------------------------|-------------------|--------------------|
|                        | Mean (SD)         | Mean (SD)          |
| 2012/1                 | 5.14 (2.29)       | 4.83 (1.21)        |
| 2012/2                 | 3.63 (1.80)       | 3.60 (0.80)        |
| 2013/1                 | 4.60 (2.87)       | 5.59 (1.86)        |
| 2013/2                 | 5.28 (2.38)       | 6.08 (1.55)        |
| 2014/1                 | 5.93 (1.98)       |                    |
ranibizumab to aflibercept for nAMD, but not for DME and RVO. The switch was expected to lead to a reduction in injection frequency for treatment-naïve patients. Rather than the anticipated decrease, injection frequency of anti-VEGF therapy increased from 2012 to 2014 in patients with nAMD (from 6.04 to 6.73), DME (5.14 to 5.93) and RVO (4.83 to 6.08). Routine treatment of nAMD in Danish clinical practice, as documented in our study, does not therefore provide clear support of the hypothesis that aflibercept has longer duration than ranibizumab and requires less frequent injections.

The increase in the mean frequency of injections could be due to better registration practices and/or improved treatment quality with more injections and/or changes in the utilization of alternative treatments (e.g. laser, steroids) prior to initiating anti-VEGF therapy and/or, for nAMD, shorter duration of aflibercept relative to ranibizumab. We were unable to test directly for this in our study, but note that anti-VEGF is the recommended first line treatment throughout the study period and the posology recommended in treatment guidelines was unchanged (for nAMD, three monthly loading doses followed by PRN where individualized dosing is given as needed depending on disease activity). That the injection frequency increased across all three indications suggests that the increase in injection frequency for nAMD is unlikely to be related to the switch to aflibercept. Instead, a likely explanation is that there has been a general trend in clinical practice in Denmark of administering more frequent injections, reflecting a shift in prescribing trends amongst ophthalmologists to optimize outcomes of anti-VEGF therapy.

Such a trend could potentially be in response to reports from real-world evidence of sub-optimal outcomes using PRN regimens. In the WAVE study, HELIOS, LUMIERE and AURA studies, and a study by the UK Writing Committee, there was a lower injection frequency of 4.34–5.7 injections over a twelve-month period than in the CATT PRN study, where patients received a mean of 6.9 ± 3.3 injections of ranibizumab over a twelve-month period. Data from the PRN clinical studies IVAN, CATT, PIER, HORIZON and SEVEN-Up have also indicated that more frequent injections produce better visual outcomes than fewer injections. Although some of these studies observed injection frequency beyond one year and our study was limited to one year, the injection frequency observed in the last period in our study is a similar frequency to the CATT study. Our results support the hypothesis that ophthalmologists may be moving towards re-treating earlier and more often, perhaps through the application of stricter re-treatment criteria, a key feature of the CATT study.

The European label for ranibizumab included PRN dosing at the time of launch. A more recent addition to the label is treat and extend dosing in 2014. Treat and extend is an individualized treatment protocol, where patients are treated at every visit but the interval between visits is extended from one month. Hence, treat and extend is associated with more injections but fewer visits than PRN. A shift in ophthalmology prescribing habits from PRN to treat and extend should increase injection frequency, similar to that seen in our study. However, treat and extend was introduced in the label of ranibizumab after the end of our study period and PRN dosing is still typically used for nAMD, RVO and DME in Denmark. Thus, the observed increase in injection frequency in our study is more likely to be related to improved monitoring leading to re-treatment, demonstrating recognition of the need to optimizing dosing to attain the best treatment outcomes.

The key strength of this study is that data were extracted from the mandatory, national treatment registry, thus
includes all patients and treatment centers. Hence, there is no selection bias on participating patients or centers. As such, results from this study are not based on a sample population, but reflect the whole population of patients receiving anti-VEGF treatment in real-world clinical practice in Denmark. This also means that any variation in treatment patterns across centers or regions will be accounted for in the results.

The main limitations of our study relate to it being retrospective and comparing treatment at different points in time, between which clinical practice may change (in addition to the change in choice of drug which is the focus of our study). However, given that the switch from ranibizumab to aflibercept happened only in nAMD, DME and RVO were used to control for external factors that could potentially influence any time trend.

The analyses are performed on a relatively small sample size, considering the total number of patients who received anti-VEGF therapy in Denmark during the study period. However, the inclusion criteria relating to loading phase were selected to allow comparison with other real-world studies of Danish patient data and to be in line with treatment guidelines in Denmark. To account for the large number of nAMD patients included due to not receiving a loading phase (616 of 1116; 55%), a sensitivity analysis was performed on all nAMD patients. The results were not sensitive to the requirement of a loading phase. Furthermore, a substantial amount of patients had other diagnoses than those included in our study. There is a risk that some of these patients were misclassified in the registry and should have been included. However, assuming that the misclassification is purely administrative and did not influence treatment, including these patients would increase the sample in the study, but not affect the estimated mean injection frequencies.

A couple of minor limitations relate to how the data were registered. In particular, it is not possible to identify whether patients receive more than one intravitreal injection in a particular calendar month or in which eye the injection was given. It is possible that a proportion of patients initiate treatment in both eyes in the same year, in which case, the injection frequency will be overestimated for these particular patients. However, this proportion is small (only an estimated 7% percent of patients), is unlikely to have changed over the study period and is unlikely to explain the upward trend in injection frequencies. Finally, while the registry contained information on anti-VEGF injection, it only contained sporadic information on which particular drug was being administered and the analysis could therefore not be conducted with this level of detail.

The results of our study are in line with other observational studies reported from different countries, including the US, France, Australia, Switzerland and Korea (Figure 3). For example, Reich et al., using real-world claims data to assess treatment patterns in Switzerland, found that there was no change in the frequency of injections between aflibercept and ranibizumab. Similar claims data from the US found there were no significant differences in injection frequency between aflibercept and ranibizumab at 6 and 12 months of therapy.

Another recent study by Rasmussen et al. examines the development of anti-VEGF injection frequency in nAMD in one Danish treatment center. In contrast to our study, they find that injection frequency decreases over time from 8.0 with ranibizumab in 2011–2012 to 6.6 with aflibercept in 2013–2014 (for patients who are treated for at least one year). While their results for aflibercept are similar to ours, they report a substantially higher injection frequency for ranibizumab. As we were not able to identify this particular treatment center in our dataset, due to its anonymized structure, we could not investigate whether the difference is due to variation in injection frequencies across treatment centers. While the study by Rasmussen et al. presents evidence on injection frequencies from only one center, the strength of our study is that it includes all centers in Denmark. Future research is needed to further explore any variation between centers.
Conclusion
This study found that the injection frequency of anti-VEGF treatment for nAMD, DME and RVO increased during the period from 2012 to 2014 in Denmark, despite a switch from ranibizumab to afibercept in nAMD. Hence, the study found no evidence for reduction in injection frequencies based on the longer duration of action of afibercept relative to ranibizumab. Instead, the results indicate that the duration of ranibizumab and afibercept is similar when used in daily clinical practice. Further research will be required to determine whether this increase of injection frequency of anti-VEGF therapy in Denmark produces better outcomes in terms of visual acuity in patients across the indications of nAMD, RVO and DME.

Notes
1. Lucentis is a registered trade name of Genentech/Novartis
2. Eylea is a registered trade name of Regeneron Pharmaceuticals/Bayer
3. Avastin is a registered trade name of Genentech/Roche

Transparency
Declaration of funding
This study was funded by Novartis Healthcare.

Declaration of financial/other relationships
H.V. has disclosed that he has acted as a consultant to Alcon Nordic, Bayer, Novartis Healthcare, and Allergan. T.K.O. and J.Z. have disclosed that they are employees of DLi Market Intelligence, a company that received funding from Novartis to help conduct this study. M.S.H. has disclosed that he is an employee of Novartis Healthcare.

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