Thirteen years of intravitreal anti-vascular endothelial growth factor therapy: the promises and burdens of a paradigm shift told from the perspective of the largest retina service in Norway.

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ABSTRACT.

Purpose: To describe the first 13 years of anti-vascular endothelial growth factor (anti-VEGF) therapy from the perspective of a public ophthalmic department serving a local community of almost one million people.

Methods: Retrospective registry study. Data from Oslo University Hospital, Norway were collected from 2006 through 2018. Hospital episode statistics were searched for episodes of care encompassing intravitreal anti-VEGF procedures. Patient-specific ID numbers, diagnoses, and drug codes were registered. In general, bevacizumab was used as first-line treatment, with aflibercept reserved for resistant cases from 2013.

Results: The number of unique patients treated per year increased from 130 in 2006 to 3428 in 2018. In 2018, 2488 (73%) patients had also received treatment the previous year. The number of yearly injections increased from 228 in 2006 to 25 570 in 2018. In 2018 the diagnosis macular degeneration constituted 69% of injections, diabetic retinopathy constituted 15%, retinal vein occlusion constituted 13%, and other diagnoses constituted 3%. In the same year 49% of injections were with bevacizumab, 46% with aflibercept, 4% with ranibizumab, and 1% with dexamethasone implants. The bevacizumab to aflibercept ratio was almost 1:1 for macular degeneration and diabetic retinopathy; for retinal vein occlusion the ratio was 13:7.

Conclusion: In 13 years there was an approximately 100-fold increase in the number of yearly intravitreal injections. A majority of patients received long-term treatment. Macular degeneration was the most common diagnosis. Using bevacizumab as first-line treatment, with aflibercept reserved for resistant cases from 2013, eventually resulted in a nearly 1:1 ratio in drug usage.

Key words: aflibercept – anti-vascular endothelial growth factor therapy – bevacizumab – intravitreal injections – ranibizumab

Introduction

Intravitreal administration of anti-vascular endothelial growth factor (anti-VEGF) medicines is commonly an unprecedented activity among the services offered in a contemporary medical retina service; yet, the history of ophthalmic anti-VEGF therapy is relatively young. While the first drug in the class, pegaptanib, was approved for intravitreal use in late 2004, the utilization of anti-VEGF biopharmaceuticals truly unfolded with off-label use of bevacizumab from 2005 and approval of ranibizumab for wet age-related macular degeneration (AMD) in 2006 (Kim & D’Amore 2012).

The first intravitreal anti-VEGF injection at Oslo University Hospital was administered in December 2005. Fortunately for the patient, a pensioner with a retinal angiomatous proliferation (RAP) in the second eye, anti-VEGF therapy brought about a paradigm shift in the management and prognosis of several prevalent retinal diseases, including the RAP lesion the person suffered from. Still, repeated bevacizumab injections were necessary, and other cases would soon follow; in the course of time, a seemingly ever-growing patient group in need for monitoring and treatment inevitably put a strain on the department’s resources.
The purpose of this study was to describe the first 13 years of anti-VEGF therapy from the perspective of the Department of Ophthalmology at Oslo University Hospital, the largest provider of retinal care in Norway.

Materials and Methods

The trial was conducted as a retrospective, single-centre registry study approved by the institutional data protection officer. Data from Oslo University Hospital, Norway were collected from 2006 through 2018. In this period the hospital’s Department of Ophthalmology provided medical retina care to nearly one million people living in the city of Oslo and the surrounding Akershus County.

Hospital episode statistics were searched for episodes of care that included the Nordic Medico-Statistical Committee’s Classification of Surgical Procedures (NCSP) code CKD05: intravitreal injection of drug. For each CKD05 episode the following parameters were registered: patient-specific ID number; 10th revision of the International Classification of Diseases (ICD-10) diagnosis; Anatomical Therapeutic Chemical (ATC) Classification System drug code; and NCSP code for right, left, or bilateral procedure (ZXA 00, ZXA 05, or ZXA 10). A bilateral procedure or the use of two different drugs was counted as two intravitreal injections. As ATC codes for bevacizumab and ranibizumab were initially not routinely registered, an overview of anti-VEGF drug proportions could be provided from 2009. Although its primary mechanism of action is not anti-VEGF mediated, the dexamethasone intravitreal implant Ozurdex (Allergan, Dublin, Ireland) was also included in the study. CKD05 episodes with other ATC drug codes, for example antibiotics, were excluded.

In the beginning of the study period, bevacizumab was generally used as first-line anti-VEGF treatment, whereas ranibizumab was used as second-line treatment at the doctor’s discretion. From November 2008 to March 2009, however, the South-Eastern Norway Regional Health Authority temporarily withdrew its support for the off-label use of bevacizumab. Afibbercept became commercially available in 2013 and was initially used as second-line treatment in treatment-resistant cases. Treatment resistance was defined anatomically as the inability to achieve recovery of macular fluid despite monthly bevacizumab injections and at least 3 months of therapy. In 2015, based on the Protocol T results from the Diabetic Retinopathy Clinical Research Network, aflibercept became first-line treatment in cases of diabetic macular oedema (DME) presenting with decimal visual acuity < 0.4 (Diabetic Retinopathy Clinical Research Network et al. 2015). The dexamethasone intravitreal implant became commercially available in 2010, and throughout the rest of the study, it was used as an alternative to anti-VEGF treatment in cases of DME or retinal vein occlusions (RVO) at the doctor’s discretion.

The data were presented annually with simple descriptive statistics. The proportions of various diagnoses or drugs were determined after excluding episodes of care missing diagnosis or drug code. The number of new patients per year was determined by excluding all patient-specific ID numbers that also received treatment the previous year. The number of yearly episodes of care per patient was determined after excluding individuals that had not completed a full year of therapy. In consequence, the first study year, 2006, was not included. The number of yearly bevacizumab or aflibercept injections per patient was determined after excluding individuals that had either not completed a full year of therapy or received both drugs within 1 year, that is might have switched treatment.

Results

The data set consisted of 7984 unique patients, 136 456 episodes of care, and 153 823 intravitreal injections over 13 years. The study’s main findings are shown in Table 1.

The yearly number of unique patients receiving treatment increased from 130 in 2006 to 3428 in 2018. In 2018 there were 940 new patients (27%), whereas 2488 patients (73%) had also received treatment the previous year (Fig. 1). The yearly number of episodes of care increased from 224 in 2006 to 22 029 in 2018 (Fig. 2); each patient had a mean of approximately seven episodes of care per year. The number of yearly injections increased from 228 in 2006 to 25 570 in 2018 (Fig. 2). In 2018, 3541 (14%) of the injections were carried out as bilateral procedures.

The most common diagnosis throughout the study was H35.3 (degeneration of macula and posterior pole), but there was a tendency towards a decreasing H35.3 proportion, whereas the opposite was true for H36.0 (diabetic retinopathy) and H34.8 (retinal vein occlusion). In 2018 the diagnosis H35.3 constituted 69% of the injections, H36.0 constituted 15%, H34.8 constituted 13%, and other ICD-10 diagnoses constituted 3%.

In 2012, the last year before aflibercept became available, 89% of the injections were with bevacizumab. From 2013 there was an increasing aflibercept proportion at the expense of bevacizumab (Fig. 3). In 2018, 49% of the injections were with bevacizumab, 46% were with aflibercept, 4% were with ranibizumab, and 1% were with dexamethasone implants. In 2018 the ratio of bevacizumab to aflibercept was almost 1:1 for the diagnoses H35.3 and H36.0; for the diagnosis H34.8 the ratio was 13.7. In the same year the mean (median) number of injections per patient was 6.7 (6) for individuals receiving bevacizumab and 8.8 (8) for individuals receiving aflibercept.
Discussion

Norway has a tax-funded public healthcare system, and intravitreal anti-VEGF treatment is centralized to clinics accessible to the general public. For that reason, comprehensive treatment activity data are readily available, and the present study provides an accurate account of realizing intravitreal anti-VEGF therapy in an ophthalmic department serving a local community of almost one million people. The results reveal a steady increase in the activity lasting throughout the study period.

Due to superior visual outcomes, anti-VEGF therapy has replaced photodynamic therapy (PDT) and laser photocoagulation as the first-line treatment for prevalent macular diseases such as wet AMD, DME, and RVO. The earlier treatment options certainly required costly laser equipment and, for PDT, concurrent use of an expensive drug, verteporfin. There are, however, important drivers of higher resource demands associated with present-day anti-VEGF therapy. First, the utilization of PDT and laser photocoagulation in macular disease was generally restricted to classic choroidal neovascularization, branch RVO, and DME. By way of comparison, anti-VEGF therapy allows for treatment of a wide range of disorders (Kwong & Mohamed 2014). Secondly, whereas the indication for repetitive PDT or laser photocoagulation was often limited, long-term anti-VEGF therapy is commonly necessary. In a previous study from our department, nearly a quarter of wet AMD patients still received follow-up care after 8 years of treatment (Berg et al. 2017). The present study showed a growing proportion of patients that had also received treatment the previous year, and towards the end of the study period, the long-term treatment courses by far exceeded the proportion of new patients.

It is beyond the scope of this study to present a comprehensive review of the controversy surrounding the ophthalmic use of bevacizumab. Still, the chronology illustrates how health governance and a bureaucratic decision to support or oppose off-label drug use can influence the choice of anti-VEGF therapy. The regional health authority withdrew its support for the off-label use of bevacizumab from November 2008 to March 2009. Accordingly, the study revealed a much lower proportion of patients who received expensive off-label treatment in 2009 as compared to the following years. For instance, bevacizumab constituted 61% of the injections in 2009 but as much as 92% in 2010. It is worth mentioning that the disagreement between Oslo University Hospital and the regional health authority over bevacizumab use led to a Norwegian multicentre study, LUCAS, comparing bevacizumab and ranibizumab for wet AMD according to a T&E protocol (Berg et al. 2015, 2016). The regional health authority requested such data to support bevacizumab use. Despite the potential for considerable regional savings, however, the initiative did not receive regional funding and was initially financed by our hospital.

The introduction of afiblercept in 2013 made a major impact on the use patterns of the various anti-VEGF drugs. Afiblercept was undeniably an extremely expensive drug compared to bevacizumab. Still, as its much greater binding affinity for VEGF and ability to bind VEGF-B and placental growth factor could translate into higher efficacy, it challenged the off-label use of bevacizumab (Heier et al. 2012). At Oslo University Hospital the debate on continued bevacizumab versus afiblercept treatment was settled by a compromise: afiblercept was reserved for treatment resistance cases. Such cases were nonetheless frequently encountered. Analogously, nearly half of the wet AMD patients in the CATT study had evidence of persistent fluid despite 2 years of monthly therapy with ranibizumab or bevacizumab (Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group et al. 2012). This CATT result well predicted the course which anti-VEGF treatment would take from 2013; eventually, almost half of the wet AMD-related injections in the present study were indeed with afiblercept, and the same was true for DME. For RVO, however, the bevacizumab proportion remained higher, suggesting that treatment resistance is less frequently encountered under these circumstances.

In a previous study from our retina service, treatment-resistant wet AMD patients that were converted to afiblercept unmistakably improved anatomically on optical coherence tomography, and the treatment burden in terms of number of injections was reduced.

Table 1. The table presents the study’s main findings. As bilateral procedures are counted as two intravitreal injections, the number of injections is higher than the corresponding episodes of care. For the mean number of episodes of care, patients that have not completed a full year of therapy are excluded; therefore, the first study year, 2006, is not included (NI).

| Year | Episodes of care | Mean episodes of care per patient | Intravitreal injections | Other diagnoses (%) | Bevacizumab (%) | Ranibizumab (%) | Afiblercept (%) | Dexamethasone implant (%) |
|------|-----------------|----------------------------------|------------------------|---------------------|----------------|----------------|----------------|------------------------|
| 2006 | 224             | 4.3     | 228                      | 14                  | 2              | Data missing | Drug not available |
| 2007 | 1561            | 5.4     | 1604                     | 2                   | 2              | Data missing | Drug not available |
| 2008 | 3008            | 6.9     | 3013                     | 4                   | 2              | Data missing | Drug not available |
| 2009 | 5122            | 7.1     | 5150                     | 6                   | 2              | Data missing | Drug not available |
| 2010 | 6577            | 6.8     | 6669                     | 3                   | 2              | Data missing | Drug not available |
| 2011 | 8615            | 6.7     | 9267                     | 4                   | 2              | Data missing | Drug not available |
| 2012 | 10715           | 7.0     | 11938                    | 5                   | 2              | Data missing | Drug not available |
| 2013 | 12415           | 7.3     | 14021                    | 6                   | 2              | Data missing | Drug not available |
| 2014 | 13230           | 7.1     | 15139                    | 7                   | 2              | Data missing | Drug not available |
| 2015 | 15126           | 7.3     | 17386                    | 8                   | 2              | Data missing | Drug not available |
| 2016 | 18069           | 7.2     | 22897                    | 9                   | 2              | Data missing | Drug not available |
| 2017 | 19725           | 7.2     | 25570                    | 10                  | 2              | Data missing | Drug not available |
| 2018 | 22029           | 7.2     | 25570                    | 11                  | 2              | Data missing | Drug not available |

H35.3 = degeneration of macula and posterior pole; H36.0 = diabetic retinopathy; H34.8 = retinal vein occlusion.
(Jorstad et al. 2015, 2017). It was, however, questionable whether a functional benefit was evident, let alone a positive cost-effectiveness of switching from less expensive treatment with bevacizumab. Bearing in mind a selection effect when a drug is reserved for treatment-resistant cases, a mean of 8.8 aflibercept injections per year in the
The present study also suggests the treatment burden could be somewhat reduced for selected patients on monthly bevacizumab by converting to aflibercept. On the other hand, the expenses associated with anti-VEGF treatment boomed following the introduction of aflibercept as second-line therapy in 2013, and aflibercept ultimately reached the fourth place on the 2018 list of total drug spending at Oslo University Hospital. By contrast, a recent review concluded that bevacizumab is the most cost-effective drug for wet AMD (Elshout et al. 2018). The falling bevacizumab proportion attributable to aflibercept represents a complex dilemma, and future drugs will likely reinforce the pressure on bevacizumab use.

Anti-VEGF therapy has become a mainstay of ophthalmic intervention. Still, the practice of repetitive intravitreal injections can be questioned. Undoubtedly, the methodology has several limitations, such as restricted treatment durability, need for frequent monitoring, and a route of administration that requires a surgical procedure to be performed. Innovative technologies that successfully address the important challenges of anti-VEGF treatment may well establish novel therapeutic principles. The present-day standard of care could even be susceptible to disruptive technologies that eventually replace the routine of intravitreal injections (Christensen. 1997). In 13 years of anti-VEGF therapy, the medical retina team at Oslo University Hospital has expanded from 5 to 14 consultants and from 11 to 26 ophthalmic nurses. There are now three injection crews working in parallel to meet the daily demand for treatment. A breakthrough that leads to greatly extended drug durability or a non-invasive route of administration, for instance, could clearly render these additional resources obsolete.

The current study has several limitations. Both incomplete coding and the ICD-10 classification’s limited level of diagnostic detail restrict an accurate interpretation of the data. Of particular note is that ATC codes for anti-VEGF drugs were not routinely registered before 2009; therefore, the proportions of bevacizumab and ranibizumab from 2006 through 2008 are unknown. Moreover, the ICD-10 code H35.3 (degeneration of macula and posterior pole) comprises wet AMD but also other retinal diseases that might be treated with VEGF inhibitors. Wet AMD is beyond doubt the prevailing

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Fig. 3. Yearly proportion of bevacizumab, ranibizumab, and aflibercept injections. Initially, drug codes were not routinely registered; therefore, data are presented from 2009. The yearly proportion of dexamethasone implants was 1–2% and is not shown. Two milestones are worthy of attention: (i) The regional health authority withdrew its support for the off-label use of bevacizumab from November 2008 to March 2009. Accordingly, the bevacizumab proportion is much lower in 2009 as compared to the following years. (ii) The introduction of aflibercept as second-line therapy in 2013 eventually resulted in an almost 1:1 ratio between bevacizumab and aflibercept.
diagnosis, but the proportions of other H35.3 diseases in the study are uncharted. Likewise, the ICD-10 code H36.0 (diabetic retinopathy) encompasses DME but also proliferative diabetic retinopathy, which may receive anti-VEGF treatment. As the study only assessed hospital episode statistics, it does not present data on visual function, the most important outcome of anti-VEGF treatment. Finally, there is a high risk of reporting anti-VEGF cost-analyses of insufficient quality and validity (Elshout et al. 2018); as the study was not designed to fulfill this aim, it does not provide analyses of treatment costs.

In conclusion, there was an approximate 100-fold increase in the number of yearly intravitreal anti-VEGF injections from 2006 to 2018. Wet AMD constituted a majority of episodes, and towards the end of the study period, long-term treatment courses by far exceeded the proportion of new patients. Using bevacizumab as first-line treatment, with aflibercept reserved for resistant cases from 2013, eventually resulted in an almost 1:1 ratio in drug usage. The increasing aflibercept proportion challenges the cost-effectiveness of treatment. In the end, the era of intravitreal anti-VEGF therapy tells the story of an ambivalent relationship between possibilities and challenges.

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