Aflibercept for treatment of wet AMD in clinical practice

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1 Summary

Age-related macular degeneration (AMD) is the most common cause of vision loss in people aged over 50 years in the western countries, and is associated with the loss of central vision and visual distortion. There are an estimated 20 000 new cases of AMD in Norway each year. Approximately 10-15% of people with AMD develop the neovascular or wet form of the disease, which is more aggressive and may lead to rapid loss of central vision. Drugs that target the vascular endothelial growth factor (VEGF) have revolutionized the treatment of neovascular age related macular degeneration (nAMD). Ranibizumab was licensed for treatment of nAMD in 2006, and in parallel doctors also started off-label use of the anti-VEGF cancer drug bevacizumab for intravitreal injections. With individualized therapeutic strategies such as treat and extend (T&E), favourable functional and anatomical outcomes can be achieved with longer injection intervals than the initially recommended monthly dosing. In some eyes, however, persistent fluid is seen despite monthly treatment with ranibizumab or bevacizumab. The novel recombinant fusion protein aflibercept, a VEGF-trap that became commercial available in 2013, has gained increasing popularity as a treatment option for eyes with persistent macular fluid despite the lack of larger randomized clinical studies evaluating the clinical results and economic consequences of this treatment strategy.

In the present thesis, we present treatment results and economic evaluations based on data from our approved internal quality register at Dep. of Ophthalmology at Oslo University Hospital monitoring patient treatment of nAMD. Patients included were those with persistent macular fluid despite monthly treatment with ranibizumab or bevacizumab that were converted to 2.0 mg aflibercept in accordance with a T&E protocol. The follow-up was 2 years, and 50 eyes from 47 patients were included. Seven eyes switched from ranibizumab
and 43 from bevacizumab. After 2 years of aflibercept treatment, structural evaluation by OCT compared to baseline showed a dry macula in 31 eyes (62%) and less macular fluid in an additional 11 eyes (22%). One eye (2%) showed no change in macular fluid, while 2 eyes (4%) showed worsening. Despite an improved anatomical appearance in the majority of eyes after conversion to aflibercept, there was no statistical improvement in vision compared to baseline over the two year period. After 2 years of aflibercept treatment, mean visual acuity was decreased equal to 3.5 letters compared to baseline (p=0.005).

Treatment burden in terms of mean number of injections was reduced from an expected 12 injections per year if bevacizumab/ranibizumab treatment was continued (contrafactual treatment) to 9.2 ± 1.5 (year 1) and 8.0 ± 2.7 (year 2) injections after converting to aflibercept. Still, at the 2 year visit 24 eyes (48%) received treatment more frequently than the recommended aflibercept label of an 8 week injection interval.

The total incremental cost of the new treatment regimen at year 1 was NOK 807 042 (actual costs minus calculated contrafactual costs). Since there was no improvement in visual acuity, the main benefit from a socio-economic perspective of this cost was the reduction of 132 consultations for the 47 patients, with a mean cost of NOK 6 133 per saved consultation at year 1. The mean cost for each saved consultation at year 2 was NOK 2 360 (incremental cost of NOK 443 661 that saved 188 consultations). The overall cost per saved consultation was calculated to NOK 3 913 over the two year period. The 47 patients experienced a mean reduction of 3.4 consultations per year over the two year period, and this reduction had a price of NOK 26 611 per patient.

In conclusion, even though the present study lack a control group, our results may question the health-economic benefit from a two year perspective of converting treatment resistant eyes from bevacizumab or ranibizumab to aflibercept in patients with nAMD.
2 Acknowledgement

As clinicians we are constantly faced with new developments in medicine such as novel drug therapies for a wide range of diseases. Even though large randomized clinical studies by the pharmaceutical companies may show beneficial effects both related to health improvement and in a health economical perspective, the everyday clinical practice using the same drug might show different results. Thus, internal quality registers are needed to continuously monitor both clinical results and economic consequences of new treatment modalities. Especially related to the issue of priority of resources in the health care sectors, these calculations are vital.

In the present thesis, the approved internal quality register for the treatment of patients with AMD at Dep. of Ophthalmology, Oslo University Hospital was utilized to evaluate the clinical and socio-economical results of switching to a new treatment strategy. The thesis is part of the Master Programme at Dept. of Health Management and Health Economics, Institute of Health and Society, Faculty of Medicine at University of Oslo.

I would like to especially acknowledge Head of Section for medical retinal disorders Øystein K. Jørstad, consultant ophthalmologist Rowan Faber and our database and statistical analysis programmer Geir Aksel Qvale for our collaboration in this project, and also all doctors, nurses and office at the department that have used all their expertise and enthusiasm to treat these patients over the years. I would also like to thank my supervisor Ivar Sønbø Kristiansen, MD PhD MPH, at Dept. of Health Management and Health Economics, University of Oslo for his valuable comments and vast interest and knowledge in health economic evaluations.
3 Abbreviations

| AMD       | Age-related macular degeneration |
| BCVA      | Best corrected visual acuity     |
| CBA       | Cost-benefit analysis            |
| CE        | Ciliary body epithelium          |
| CEA       | Cost-effectiveness analysis      |
| CUA       | Cost-utility analysis            |
| ICER      | Incremental cost-effectiveness ratio |
| logMAR    | Logarithm of the minimal angle of resolution |
| nAMD      | Neovascular age-related macular degeneration |
| OCT       | Optical coherence tomography     |
| PIGF      | Placental growth factor          |
| RGCs      | Retinal ganglion cells           |
| RPE       | Retinal pigment epithelium       |
| SD-OCT    | Spectral domain optical coherence tomography |
| T&E       | Treat and extend protocol        |
| VEGF      | Vascular endothelial growth factor |
4 Content

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5 Introduction

5.1 The Retina

The retina is the light sensory component of the eye and lines its inner surface. The retina is involved in phototransduction, which is the detection and conversion of light energy received as photons into electrical signals in the form of action potentials, which are subsequently transmitted to the visual cortex in the brain. Retinal degenerative diseases are the leading cause of visual impairment and blindness. In adult humans, the retina is considered to have limited regenerative capacity, and retinal injury results in permanent damage for which there are currently no definitive curative treatment options.

The retina consists of neurons and glial cells organized in distinct layers (Fig. 1) (Hildebrand and Fielder, 2011). The outermost layer, the retinal pigmented epithelium (RPE), is a single layer of highly pigmented epithelial cells. Together with the Bruchs membrane, the RPE forms the outer blood-retina barrier, which separates the neural retina (NR) from the underlying choriocapillaris. Additional RPE functions include

Figure 1 Schematic section of the adult human eye and retinal anatomy and neural circuitry (modified from (Hildebrand and Fielder, 2011)).
phagocytosis of photoreceptor outer segments; recycling of vitamin A; secretion of growth factors, antioxidants, and immunomodulatory cytokines; and the absorption of scattered light. The photoreceptor layer consists of the outer segment of photoreceptor cells containing the photon-capturing photopigments. There are two main types of photoreceptor cells, rods and cones. Rods contain the photopigment rhodopsin, are highly light sensitive and achromatic, and are responsible for low-resolution vision in low-light conditions. Cones require more light and are responsible for colour vision and increased temporal and spatial resolution under conditions of higher light intensities, such as daylight. There are three different cones, which are classified according to the absorption spectrum of their photopigments. The cones contain short wavelength-sensitive (S), medium wavelength-sensitive (M), or long wavelength-sensitive (L) opsin, which detects blue, green, and red colours, respectively. Photoreceptors make connections with bipolar cells that take the signals from the outer retina to the inner retina where they make connections with the retinal ganglion cells (RGCs). RGCs then extend their axons into the nervefiber layer further forming the optic nerve, which then transmits visual information to the brain. In addition, horizontal, amacrine and interplexiform interneurons modulate the electrical response in the outer and inner retina, respectively. Müller cells extend across all layers, forming both the outer and inner limiting membrane, and are essential for structural support and maintaining the extracellular environment. Additional glial cells found in the retina are astrocytes, microglia and oligodendrocytes. The cellular complexity is increased by the existence of more than 50 different subtypes of retinal neuronal cells, which have highly heterogeneous transcriptomes (Siegert et al., 2012).

At the ora serrata, the junction between the neural retina and pars plana of the ciliary body epithelium (CE), the retina is reduced to a single layer, which becomes the non-pigmented CE. The RPE is continuous with the pigmented CE. The outer retina is supplied by the choroidal circulation, which is separated from the RPE by the Bruchs membrane, while the
inner retina is supplied by the retinal circulation entering and exiting from the optic nerve. Tight junctions located between retinal endothelial cells forms the inner retinal barrier. Both the inner and outer retinal barriers are important for maintaining the retinal microenvironment.

5.2 Age-related macular degeneration (AMD)

Age-related macular degeneration (AMD), the most common cause of central vision defects in the elderly of the Western countries, is attributed to a complex interaction of genetic and environmental factors (Kinnunen et al., 2012). There are an estimated 20,000 new cases of AMD in Norway each year, and it is estimated that more than every tenth person over the age of 70 has lost their reading vision due to AMD (www.blindeforbundet.no). The disease is characterized by degeneration involving the retinal photoreceptors, retinal pigment epithelium and Bruch’s membrane, as well as alterations in choroidal capillaries leading to loss of central vision and visual distortion (Fig. 2).

Loss of central vision can affect both patients’ function and participation in ordinary daily activities. Central vision loss may also increase the risk of injuries such as falls, and thereby also fractures and complications of these (Mitchell and Bradley, 2006). Changed demographics with a growing aging population are likely increasing the number of patients with nAMD in the coming years. This growing population emphasizes the importance of increased knowledge about the disease and treatment, its consequences and challenges (Lord and Dayhew, 2001).

There is a polygenic basis for AMD, and the most significant risk factor is age, which is mediated by gradual cumulative damage to the retina and associated structures due to
oxidative stress and inflammation. Other risk factors include previous surgery, smoking, obesity, sunlight, and cardiovascular disease (Kinnunen et al., 2012). A strong genetic predisposition, which most commonly localizes 1q25-31 and 10q26 chromosomes, has been linked to AMD. The first associations observed were between the Y402H polymorphism (rs1061170) of the complement factor H gene and AMD in several populations (Kinnunen et al., 2012). Later, an association between the LOC387715/HTRA1 locus and AMD in populations of different origin has been documented.

**Figure 2.** A. Schematic representation of protein aggregation in aged retinal pigment epithelial cells (RPE). RPE digest retinal outer segment discs that are endocytosed and fused with lysosomes to be degraded. In aged RPE, lysosomal degradation is impaired resulting in accumulation of lipofuscin that is auto-oxidant material increasing oxidative stress and protein damage in the RPE cells. (Kinnunen et al., 2012) B. Dry AMD and C. Neovascular or wet AMD. (From Centre for Eye Research Australia, www.slideplayer.com).

### 5.2.1 Dry AMD

There are two main types of AMD, wet (neovascular) and dry (non-neovascular). Dry AMD is characterized by RPE atrophy due to apoptosis (Albert et al., 2015, Petrovski et al., 2007, Kinnunen et al., 2012), which cause large areas of RPE loss known as geographic atrophy. Early AMD is associated with changes in the Bruchs membrane and RPE, as well as by the accumulation of drusen; extracellular deposits of proteins and lipids that are normally phagocytosed by the RPE (Ding et al., 2009, Khandhadia et al., 2012). Areas of RPE atrophy are usually associated with areas of hyperpigmentation due to compensatory RPE proliferation in the periphery of these areas. Loss of RPE causes secondary photoreceptor
death, thinning of the retina, and gradual visual deterioration. Currently there are no well-documented treatment options for dry AMD, although intake of antioxidants has in some studies shown to be disease protective (Kinnunen et al., 2012).

5.2.2 Neovascular (wet) AMD

Approximately 10-15% of people with AMD develop the neovascular or wet form of AMD (nAMD), which is more aggressive and may lead to rapid loss of central vision. (Bressler and Bressler, 1995, Bressler et al., 1988). Excessive expression of vascular endothelial growth factor (VEGF) by RPE cells are known to be one of the leading mechanisms of new vessel formation originating from the choroid and extending through defects in the Bruch’s membrane and the RPE sub- and intraretinal. Choroidal neovascularization arise as capillary-like structures with multiple points of origin that usually causes serous detachment of the RPE or retina, RPE tears, haemorrhages and lipid exudation. Untreated nAMD is one of the leading causes of blindness and severe vision loss in the western elderly population (Lord and Dayhew, 2001) (Bressler and Bressler, 1995)

Although nAMD is found in only 10-15% of patients with AMD, the neovascular type accounts for more than 80% of cases with severe visual loss (Jager et al., 2008). Vision loss occurs through the structural and metabolic damages caused by exudates and haemorrhages, and the secondary reactive gliosis and cell death (Kinnunen et al., 2012).

5.2.3 Anti-VEGF treatment of wet AMD

Until 1999, laser photocoagulation was the only treatment for nAMD that had been shown to reduce the risk of vision loss, but with limited clinical effect. At that time, the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study reported that
photodynamic therapy (PDT) with verteporfin (Visudyne®) reduced the risk of moderate to severe vision loss for at least 5 years in patients who presented with certain subclassifications of nAMD (Bressler, 2001). While PDT somewhat improved the results seen with laser photocoagulation, there remained a pressing need for better treatment modalities. One of the most exciting advances in the treatment of nAMD came with the introduction of ranibizumab (Lucentis®) in 2006 (Rosenfeld et al., 2006). Ranibizumab is a recombinant produced, humanized, antibody (Fab) fragment that binds VEGF. The MARINA-study was a randomized, double-masked, sham-controlled clinical trial of 716 patients with minimally classic or occult CNV secondary to AMD treated with one of two different doses of intravitreal ranibizumab or sham injections given every 4 weeks for 2 years (Rosenfeld et al., 2006). The results of this study were revolutionary with 94.6% of patients treated with ranibizumab 0.5 mg experiencing vision stabilization or improvement compared with 62.2% of patients receiving sham injections. These results were further supported by the ANCHOR study (Brown et al., 2006) showing that 96.4% of patients treated with 0.5 mg ranibizumab lost less than 15 letters of vision compared with 64.3% of patients treated with PDT at 1 year. The results of these trials resulted in anti-VEGF therapies largely replacing previous treatment modalities.

Bevacizumab (Avastin®) is a full-length monoclonal antibody that binds all isoforms of VEGF-A, and was originally approved in 2004 for the treatment of metastatic colorectal cancer. Soon thereafter, physicians started to use it off-label as an intravenous or intravitreal treatment for nAMD. Despite the lack of clinical research to support its safety or efficacy, anecdotal evidence led to its widespread popularity prior to the approval of ranibizumab in 2006. The drug cost for each vial of Lucentis® is currently NOK 7107 (medicinal product purchasing collaboration price 2016) compared to approximately NOK 300 for multiple compounded syringes of Avastin®, which dramatically lowers the cost of this drug. To
address the safety and therapeutic concerns of the widespread, off-label use of Avastin in the treatment of wet AMD, the National Eye Institute commissioned the CATT trial (Martin et al., 2011). This multicentre, single-blind, non-inferiority trial, with 1208 patients with neovascular AMD, demonstrated that bevacizumab was equivalent to ranibizumab both with respect to effect and with no certain conclusions regarding side effects in the 1-year data. With individualized therapeutic strategies such as treat and extend (T&E) (Fig. 3), favourable functional and anatomical outcomes can even be achieved with longer injection intervals than the initially recommended monthly dosing (Berg et al., 2015, Berg et al., 2016).

**Figure 3.** Treat and extend (T&E) strategy. As long as the retina is dry, the interval between injections are extended, but if the retina becomes wet (macular oedema), the treatment interval is reduced (Berg et al., 2015).

In other cases, however, persistent fluid is seen despite monthly treatment with ranibizumab or bevacizumab. After 2 years in the CATT study, 51.5% of eyes receiving monthly ranibizumab and 67.4% of eyes receiving monthly bevacizumab still had macular fluid present on optical coherence tomography (OCT). Thus, due to large capacity problems and
increasing costs of AMD treatment, the ophthalmological society are desperately seeking novel drugs that can be administered either with an non-invasive technique (such as eye drops) or drugs that can be given with longer intervals.

The recombinant fusion protein aflibercept, a VEGF-trap, (Fig. 4) represents a promising therapeutic option for these treatment resistant sub-groups. Aflibercept (Eylea®) is a member of Regeneron’s proprietary family of ‘Trap’ products that catch, hold, and block (i.e. trap) certain cytokines and was originally developed for cancer therapy.

Figure 4. Aflibercept (VEGF Trap) was created by fusing the second VEGF-binding domain from VEGFR1 and the third VEGF-binding domain from VEGFR2 to the Fc backbone of an IgG1 molecule. The resultant soluble receptor has a very high affinity ($K_D < 1$ pM) for VEGF165. From: http://www.expert-reviews.com/doi/full/10.1586/ecp.12.81.

The eye formulation, also referred to in the literature as VEGF Trap-Eye, is identical in structure to the intravenous cancer treatment, with further purification steps and buffer modification to allow for comfortable, non-irritating intravitreal injection. Unlike currently available anti-VEGF therapies, aflibercept, in addition to binding to all VEGF-A isoforms and VEGF-B, also binds to placental growth factor (PIGF) (Papadopoulos et al., 2012). Like VEGF, PIGF is present in human CNV membranes, and animal studies have shown that PIGF contributes to the development of experimental nAMD. Another differentiating feature of aflibercept is that the binding affinity for VEGF is 0.5 pM Kd, which is considerably stronger than ranibizumab, bevacizumab, or native VEGF receptors. This allows for effective blocking of VEGF even at low concentrations, which may potentially translate into a longer duration of action and extended dosing intervals. Some years ago, the first phase III randomized clinical
studies comparing aflibercept with ranibizumab were published (Heier et al., 2012). This study showed that there was no statistical significant difference in clinical effect after 1 year when aflibercept was given with 8 weeks interval after an initial 3 loading doses while ranibizumab was given with 4 weeks interval. This could theoretically significantly decrease the burden of treatment both for the patients and the health care system by reducing the number of yearly injections. However, compared to off-label use of Avastin®, the price of each aflibercept (Eylea®) vial of NOK 7290 (medicinal product purchasing collaboration price 2016) is 24 times more expensive and in the same price range as Lucentis®.

5.3 Economic evaluations in treatment of wet AMD

Nobel-prize winning Chicago-school economist Milton Friedman is famous for saying "There is no such thing as a free lunch." Although Norwegian patients are provided with seemingly “free” health care, there are considerable economical costs for the Norwegian society of producing it (Olsen, 2009). The more a particular treatment costs, the fewer resources are left for other treatments. Thus, comparisons of costs with outcomes are needed. When new and cost-expensive drugs such as aflibercept comes available, the incremental drug costs related to both treatment effects and the putative reduction in treatment burden for the health-care system and the patient should be estimated.

A full economic evaluation can be defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences (Drummond, 2005). The basic tasks of any economic evaluation is to identify, measure, value and compare costs and consequences of the alternatives being considered in an incremental analysis, i.e. the difference in costs is compared with the difference in consequences. The main costs arise from resources used by the health-care system (mainly drug costs and salary), resources used by the patients and their
families, resources used in other sectors and any potential changes to productivity. Drummond has suggests four points that need to be accessed in order to include the right costs in an economical evaluation (Drummond, 2005):

- What is the viewpoint of the analysis – a socio-economic analysis compared to analysis for an individual or an organization? If a socio-economic analysis is chosen, expenses for travel to and from examinations at the hospital can be excluded.
- If only two or more programs are to be compared, cost common to both or all alternatives can be excluded.
- If some costs are likely to be reflected through other costs and it is likely that these costs will not influence the choice between the different programs, these costs can be excluded.
- If a cost due to their low magnitude is unlikely to affect the decision they can be deleted but this exclusion needs to be justified in the analysis.

Furthermore, it is important to consider whether valuation of non-market items (e.g. volunteer time, patients/family leisure time) should be included. It is also important to distinction between non-monetary health improvements and monetary productions gains. When health benefits are measured in money they are referred to as cost-benefit analysis (CBA). This approach allows the analyst to compare the incremental cost of the program with its incremental cost in commensurate units of measurement. If benefits are not measured in money, cost-effectiveness analysis (CEA) is being used. CEA examines both the costs and the health outcomes of alternative health programs. The results of CEA are usually expressed as a cost-effectiveness ratio (e.g. “cost per case detected”, “costs per life year gained”). One particular type of CEA analysis is cost-utility analysis (CUA), where benefits are measured as a parameter of individual utility from health (Olsen, 2009). An increased quality of life is expressed as a utility value on a scale from zero (dead) to one (perfect quality of life). As for
CEA, CUA requires reliable effectiveness data. But as opposed to CEA, only final effectiveness data like lives saved, or disability-years averted can be used. The ratio between incremental effect and incremental costs is refers to as the incremental cost-effectiveness ratio (ICER) (Olsen, 2009). Importantly, since ICER only is monitoring differences is costs and effects, it is vulnerable to which treatment option is selected for comparison. If the existing therapy is ineffective or very expensive, the ICER of a new treatment modality with an ineffective cost-utility ratio will appear with a high ICER ratio. Similarly, if the existing therapy is effective and inexpensive, it will be difficult to gain a high ICER for a new treatment modality. In the field of ophthalmology, this might explain why the expensive alternative ranibizumab usually are selected for CUA for new treatments modalities and not the inexpensive alternative bevacizumab.

In addition to health economic analysis prior to implementation of new treatments, it is also vital to follow the real-life economic consequences after implementation both on the level of an individual, the health-care system and from a socio-economic perspective, and relate these calculations to the actual clinical results of the change in treatment. This can be achieved through creating internal quality registers where key information about clinical outcome and the use of hospital resources are continuously registered and data from the register are regularly being processed and evaluated. In the current thesis, the 2 year results of our internal quality register to monitor functional, anatomical and economic effects of converting to aflibercept in wet AMD patients with persistent macular fluid despite monthly treatment with ranibizumab or bevacizumab are presented.
6 Methods

6.1.1 Internal quality register for treatment results

When aflibercept became commercially available in Norway in May 2013 all consenting nAMD patients in our clinic with any fluid in the macula, subretinally or intra-retinally, despite monthly treatment with ranibizumab or bevacizumab were converted to 2.0 mg aflibercept. At the same time a prospective single-centre quality registry, approved by the Oslo University Hospital, was created to study the results. In the present study, we have included the first 50 eyes in the internal quality register with the following criteria; patients had to previously been diagnosed with exudative AMD with angiographic evidence of a classic or occult membrane or a retinal angiomatic proliferation. Previous treatment with ranibizumab or bevacizumab had to have lasted for at least 6 months, and as a minimum, the 3 last injections before conversion had to have been given monthly. A deviation from the defined injection intervals of +/- 1 week was allowed. Of these 50 eyes, both eyes from 3 patients were included.

Patients received 2.0 mg aflibercept in accordance with a T&E strategy. Monthly injections were given as long as residual macular fluid was present on OCT. If a dry macula was achieved, the injection interval was extended by 2 weeks at the time. Recurrent disease was defined as any macular fluid on OCT or new macular haemorrhage. If examination showed sign of recurrence, the injection interval was consecutively reduced by 2 weeks until a dry macula was achieved again and/or the macular haemorrhage was absorbed. The injection interval was thereafter again extended by 2 weeks at a time, but with a maximum final injection interval 2 weeks shorter than the interval causing recurrent disease (Berg et al.,
A change of treatment strategy with monthly observation, or repeated injection only “as needed” was permitted if the macula stayed dry after a 12 week injection interval. We defined treatment failure as no anatomical improvement on OCT after at least 3 monthly aflibercept injections. Reintroduction of previous anti-VEGF therapy, or rescue treatment was allowed if an eye met the criteria for treatment failure. Eyes that underwent cataract surgery and YAG laser capsulotomy during the 2 years of follow-up were excluded from the study.

The patient’s age, sex, prior numbers of injections, duration of treatment and anti-VEGF medication (bevacizumab or ranibizumab) at baseline were registered at inclusion in the internal quality register. Primary effect outcomes were visual acuity, anatomical oedema on OCT and injection frequency. We defined baseline as the point in time of switching to aflibercept treatment. Data were collected at baseline, at the first visit after 1 year and at the first visit after 2 years of aflibercept treatment. Best-corrected visual acuity (BCVA) was obtained from a ClearChart (Reichert Technologies, Depew, NY) digital acuity test and converted to logarithm of the minimal angle of resolution (logMAR) for statistical analysis.

As opposed to decimal visual acuity an increasing logMAR score represents decreasing visual acuity; a logMAR score of 0.00 represents full normal vision, a logMAR value of >0.5 represent a vision defined as severely vision impaired and a logMAR value of 1.00 is considered to be legally blind with respect to central vision. For individual eyes we defined that a BCVA difference ≥0.1 logMAR equal to 5 letters represented a clinically important difference, while a difference <0.1 logMAR represented a clinically stable BCVA (Beck et al., 2007). BCVA from eyes receiving rescue treatment was not included. Twelve radial SD-OCT scans of the macula were performed at each visit on a RS-3000 OCT Retinascan (NIDEK CO., LTD., Gamagori, Japan).
6.1.2 Economic analysis

The costs to be included in evaluating the effect of implementation of aflibercept can be divided into the following cost items: health sector costs; costs on other (public) sectors; patient/family (time) costs and productivity losses (Drummond, 1997, Drummond, 2005). In addition, we also estimated the contrafactual costs, i.e. costs if ranibizumab/bevacizumab treatment had been continued for the 2 year period instead of switching to aflibercept. In the present thesis, we have chosen a socio-economic evaluation of the implemented treatment, i.e. we will not include factors only valid for an individual or the health-care organization.

Health sector costs

Due to lack of capacity at daytime in the Eye clinic, all alterations in injections frequency of the patients will only lead to changes in the need for project-based evening work for doctors, nurses and office personnel. The project cost per evening, that included the evaluation and injection of 40 patients is at present 6500 NOK per doctor (7 doctors/evening, 5 for evaluation of the patients and 2 for injections), 3000 NOK per nurse (3 for pre-evaluation and 2 for injection assistance) and 2800 for office (2 for administration). In addition, each value is multiplied by 1.3 for social costs.

For drug calculations, the 2016 prices from the Medicinal product purchasing collaboration (LIS) for aflibercept were NOK 7290 while 1 vial of ranibizumab had a cost of NOK 7107. When aflibercept became available in 2013, we made a protocol for splitting aflibercept vials into 2 syringes under sterile conditions, so that the actual drug cost for aflibercept for the two year period was calculated to NOK 4037 per injection (due to quality control and logistics we were not able to split all vials into two syringes). For bevacizumab, an ampulla containing 4 ml have a cost of NOK 3607 (Felleskatalogen.no), and this was compounded under sterile
conditions into multiple syringes so that the price per injection of NOK 330 were used for the calculations.

Income from performance-based financing (DRG) was not included in the estimate, as this expense from the government/income for the Hospital is cancelled out in a socio-economic evaluation.

**Costs on other (public) sectors**

Travel-cost to and from examinations at the hospital was excluded from the calculation due to the socio-economic perspective where only fuel-costs are considered of interest (not included).

**Patient/family (time) costs and productivity losses**

If aflibercept treatment potentially would significantly decrease the number of visits the hospital for the patients, the new treatment modality will decrease hospital time for the patients and this could be calculated as an improvement in production loss for employees of the patients or as improved leisure time for those who do not work. As previously described, due to lack of capacity at daytime in the clinic, all alterations in injections frequency of the patients will only lead to changes in the need for project-based evening consultations. In addition, the average age of nAMD patients is close to 80 years, so there will be very little changes in productions loss from the patient perspective after a potential more effective treatment is introduced. We have thus not included changes in production loss. In addition, we have not tried to calculate a value of improved leisure time resulting from a putative decreased number of doctor visit, however, it is important to bear in mind this when evaluating the results.
**Contrafactual costs and clinical results**

One important aspect of monitoring treatment results is to compare the observed results to those you would expect if the intervention had not been implemented - this is known as the 'counterfactual' (Holland et al., 1986, Maldonado, 2016). If aflibercept was not introduced in our clinic for treatment resistant macular oedema on previous bevacizumab/ranibizumab, we assume that these patients would have needed monthly injections with their prior medication due to persistent macular oedema according to the T&E protocol, and contrafactual drug costs and number of consultations are based on this estimation. Regarding the natural history of disease progression (contrafactual disease progression), the results from our quality register was compared with other studies in the literature describing anatomical and functional outcome on monthly bevacizumab/ranibizumab treatment despite persistent macular oedema (Mantel et al., 2016).

**Statistical analysis**

Data are presented as mean (SD) for continuous and n (%) for categorical variables. The baseline descriptive data of age, number of months and injections of prior treatment are given as mean (range) because that is considered the clinical important information. Data were normally distributed, and paired samples t-tests were used for statistical analysis using the IBM-SPSS (IBM-SPSS, Inc., Chicago, IL) software version 22.0. For individual eyes we defined a clinically important visual difference as a BCVA difference of $\geq 0.1$ logMAR, equal to 5 letters, while a difference $<0.1$ logMAR represented a clinically stable BCVA.
7 Results

50 eyes from 47 patients fulfilled the inclusion criteria for the study. At baseline the eyes had received a mean (range) of 29 (6-74) prior injections over a time period of 38 months (6-81). 43 eyes were converted from bevacizumab and 7 from ranibizumab. Mean BCVA was 0.25 ± 0.15 logMAR at baseline. The main clinical results are summarized in Table 1.

Table 1 Main clinical results.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After 1 year of aflibercept</th>
<th>After 2 years of aflibercept</th>
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<tbody>
<tr>
<td>LogMAR visual acuity, mean ± SD</td>
<td>0.25 ± 0.15</td>
<td>0.24 ± 0.14 (p=0.531)</td>
<td>0.32 ± 0.21 (p=0.005)</td>
</tr>
<tr>
<td>Number of eyes with dry macula, n (%)</td>
<td>Baseline 0 (0%)</td>
<td>After 1 year of aflibercept 22 (44%)</td>
<td>After 2 years of aflibercept 31 (62%)</td>
</tr>
<tr>
<td>Number of aflibercept injections, mean ± SD</td>
<td>1st year of aflibercept 9.2 ± 1.5</td>
<td>2nd year of aflibercept 8.0 ± 2.7 (p=0.013)**</td>
<td></td>
</tr>
</tbody>
</table>

* 5 eyes (10%) did not complete 2 years of aflibercept treatment due to treatment failure.

** compared to 1st year
The majority of eyes showed improved anatomic outcomes after converting to aflibercept; after 2 years of aflibercept treatment structural evaluation of individual SD-OCT compared to baseline showed a dry macula in 31 eyes (62%) and less macular fluid in an additional 11 eyes (22%). One eye (2%) showed no change in macular fluid, while 2 eyes (4%) showed worsening. 2 eyes (4%) had received rescue treatment during the second year of follow up.

Treatment burden in terms of mean number of injections was reduced from an expected 12 injections per year if bevacizumab/ranibizumab treatment was continued (contrafactual treatment) to $9.2 \pm 1.5$ (year 1) and $8.0 \pm 2.7$ (year 2, $p=0.013$ compared to the first year) injections after converting to aflibercept. At the 2 year visit, 24 eyes (48%) received treatment more frequently than the recommended aflibercept label of an 8 week injection interval.

Despite an improved anatomical appearance after conversion to aflibercept, there was no statistical improvement in vision compared to baseline over the two year period. After 2 years of aflibercept treatment, mean BCVA was $0.32 \pm 0.21$ logMAR representing a small decrease in visual acuity equal to 3.5 letters lost compared to baseline ($p=0.005$). Five eyes (10%) had a clinically important improvement, defined as BCVA difference $\geq 0.1$ logMAR equal to 5 letters, and 14 eyes (28%) had a clinically important decline in BCVA equal to at least 5 letters. BCVA remained clinically stable, defined as a difference $<0.1$ logMAR, represented a clinically for 26 eyes (52%).

The total calculated of drug – and administrative costs by switching from the presumed monthly treatment of bevacizumab/ranibizumab (contrafactual costs) to aflibercept administered using a T&E protocol is presented in Table 2. The total incremental cost of the new treatment regimen at year 1 was NOK 807,042 (actual costs minus calculated contrafactual costs). Since there was no improvement in visual acuity, the main benefit from a socio-economic perspective of this incremental cost was the reduction of 132 consultations.
for the 47 patients, with a mean cost of NOK 6 133 per saved consultation at year 1. The mean cost for each saved consultation at year 2 was NOK 2 360 (incremental cost of NOK 443 661 that saved 188 consultations). The overall cost per saved consultation was calculated to NOK 3 913 over the two year period. The 47 patients experienced a mean reduction of 3.4 consultations per year over the two year period, and this reduction had a price of NOK 26 611 per patient from a socio-economic perspective.

Table 2. Contrafactual and actual costs of switching patients with neovascular AMD and treatment resistant macular oedema from monthly ranibizumab/bevacizumab to aflibercept administered using a Treat and Extend protocol.

<table>
<thead>
<tr>
<th>DRUG COSTS</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrafactual costs (NOK):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab every 4. week, 43 eyes</td>
<td>170 280</td>
<td>170 280</td>
<td>340 560</td>
</tr>
<tr>
<td>Ranibizumab every 4. Week, 7 eyes</td>
<td>596 988</td>
<td>596 988</td>
<td>1 193 976</td>
</tr>
<tr>
<td>Actual costs:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aflibercept T/E protocol, 50 eyes</td>
<td>1 857 020</td>
<td>1 614 800</td>
<td>3 471 820</td>
</tr>
<tr>
<td><strong>Difference in drug costs (NOK)</strong></td>
<td>-1 089 752</td>
<td>-847 532</td>
<td>-1 937 284</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CONSULTATIONS</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrafactual number of consultations:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly consultations, 47 patients</td>
<td>564</td>
<td>564</td>
<td>1 128</td>
</tr>
<tr>
<td>Actual number of consultations:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eylea T/E protocol, 47 patients</td>
<td>432</td>
<td>376</td>
<td>808</td>
</tr>
<tr>
<td>Total reductions in consultations</td>
<td>132</td>
<td>188</td>
<td>320</td>
</tr>
<tr>
<td><strong>Difference in salary hospital staff (NOK)</strong></td>
<td>282 710</td>
<td>403 871</td>
<td>686 581</td>
</tr>
<tr>
<td><strong>Incremental cost of new treatment (NOK)</strong></td>
<td>-807 042</td>
<td>-443 661</td>
<td>-1 250 703</td>
</tr>
</tbody>
</table>
8 Discussion

Health care decision makers, such as a head of an ophthalmological unit, are constantly faced with comparisons between a new treatment and the current treatment, and thus needs to access the incremental costs between the new and the existing treatment compared with their incremental effects. Treatment with intravitreal anti-VEGF makes it possible for many patients to maintain adequate visual acuity and significantly reduces the number of patients who are functionally blind also in the Nordic countries (Heier et al., 2012) (Bloch et al., 2012). However, this treatment is extremely resource-intensive to outpatient clinics and patients due to the need for frequent consultations. When new and more cost-expensive drugs such as aflibercept comes available, one thus has to evaluate the incremental drug costs related to both treatment effects and the putative reduction in treatment burden for the health-care system. Prior to implementation of new treatment, the company-based randomized clinical studies including health economic analysis (Heier et al., 2006, Heier et al., 2012), economic analysis based on national data (Samdal, 2007) as well as standardized evaluations of the present knowledge base in form of Health Technology Assessments (HTA) (Moe, 2013) should lay the ground for decision making. However, equally important is to follow-up with estimation of the factual outcome by creating internal quality registers (Jorstad et al., 2015) monitoring the actual clinical effects and economic consequences of the new treatment modality.

In the present thesis we have presented 2 years data from our internal quality register monitoring functional, anatomical and economic effects of converting to aflibercept in wet AMD patients with persistent macular fluid despite monthly treatment with ranibizumab or bevacizumab. Treatment in accordance with a T&E strategy makes the study particularly
relevant as this regimen seems to be the most favoured in clinical practice today (Patel et al., 2015). After 2 years of follow-up, we found a significant anatomical improvement for a majority of eyes. While visual acuity remained unchanged from baseline at year 1 there was a small decrease in mean visual acuity during the second year, though few eyes experienced a clinically important decline in visual acuity. These findings are in coherence with our previous short-term clinical data (Jorstad et al., 2015) as well as the first systematic meta-analysis evaluating the visual and anatomical outcomes of patients with resistant AMD converted to aflibercept (Seguin-Greenstein et al., 2016). This meta-analysis of four retrospective and three prospective studies provides substantial evidence for a significant anatomical effect of converting to aflibercept, but the effect on visual function was far more modest.

One important task involved in evaluating new treatments is to compare the observed results to those you would expect if the intervention had not been implemented – or the contrafactual results (Maldonado, 2016, Holland et al., 1986). Without a control group, it is impossible to develop an accurate estimate of what would have happened in the absence of an intervention since this is based on a series of local factors related both the individual patient population and the health-care system. However, comparing our results with the literature may give important indications about the contrafactual clinical outcome. A recently published 1 year pilot study (Mantel et al., 2016) exploring the effect of converting eyes with exudative AMD requiring monthly ranibizumab therapy to aflibercept compared to continuing ranibizumab therapy, found that mean visual acuity decreased by 2.0 ETDRS letters in the aflibercept group and by 0.5 EDTRS letters in the ranibizumab group after 1 year of observation, a difference that was nearly significant ($p = 0.07$). In the Norwegian multicentre study LUCAS, visual acuity decreased in the bevacizumab group by 1.3 letters from year 1 to year 2, and by 1.8 letters in the ranibizumab group (Berg et al., 2016). Taken together, these data indicate
that the contrafactual clinical results regarding visual acuity by not switching our patients to aflibercept would probably not differ significantly from the actual results after 2 years of aflibercept treatment. Furthermore, this suggests that continuous AMD progression of dry, atrophic changes are as important as persistent exudation in explaining a decrease in visual function. Furthermore, we do not know the consequences of repetitive anti-VEGF inhibition on normal retinal/choroidal physiology over time. It is also not known whether a strategy that aims to resolve all macular fluid achieves the best long term functional outcome. An ongoing study that compares functional results between a treatment strategy that tolerates small amounts of subretinal fluid, and, intensive treatment with no tolerance of fluid, might provide new insights into retreatment criteria for managing exudative AMD (Arnold et al., 2016).

Given that the contrafactual – and actual clinical results probably would have been in the same range regarding visual acuity and thus health outcome for the patient, the incremental costs related to changes in treatment burden is considered most relevant in a socio-economic evaluation of this new treatment protocol. The growing number of patients and high cost of treatment for nAMD poses a serious burden on health care systems. Until more effective medications are introduced, the challenge is to avoid undertreating patients, which could result in irreversible vision loss. Since aflibercept, at least in the company-sponsored clinical trials (Heier et al., 2012), showed similar clinical results with 8 weeks intervals as monthly ranibizumab injections, this might reduce the treatment burden both for the patient and the health care system defending a significant increase in drug cost compared to off-label use of bevacizumab. However, in the present study, after 2 years of aflibercept treatment many eyes required more frequent treatment than the recommended aflibercept label of 8 week injection intervals, and as pointed out, with no improvement in visual acuity compared to the estimated contrafactual outcome. Thus, one could argue whether the calculated reduction from 12 yearly consultations per patient to 9.2 and 8.0 respectively (an average reduction of 3.4 visits
per patient/year), and with a total price of NOK 26 611 per patient over the two year period is considered a cost-beneficial treatment from a socio-economic perspective.

Our study has some important limitations. Firstly, in line with the studies in the mentioned meta-analysis, due to the fact that these data are based on an internal quality register and not a clinical research protocol, we lack a control group and thus have to rely on calculations of the contrafactual outcome. Furthermore, the eyes converted to aflibercept are heterogeneous in regard to both previous treatment duration and anti-VEGF therapy, reflecting the study’s real-life setting. In addition, our sample size is relatively small and inclusion of both eyes from 3 patients may violate the assumption of data independency.

In conclusion, based on data from our internal quality register a majority of eyes with persistent macular fluid despite monthly treatment with ranibizumab or bevacizumab showed improved anatomic outcomes two years after converting to aflibercept using a T&E strategy. However, there were no statistical improvements in vision compared to baseline over the two year period, and a small decrease in mean BCVA equal to 3.5 letters after the second year of treatment. This is in coherence with expected natural history of disease progression if the anti-VEGF treatment at baseline was continued. The 47 patients experienced a mean reduction of 3.4 consultations per year over the two year period, and this reduction of visits had a price of NOK 26 611 per patient. Even though we do not have a control group in the present study and estimations of contrafactual clinical results – and costs are hampered with uncertainty, our results may question the health-economic benefit of converting treatment resistant eyes from bevacizumab to aflibercept in patients with wet AMD.
9 References


JORSTAD, O. K., FABER, R. T. & MOE, M. C. 2015. Initial improvements when converting eyes with treatment-resistant exudative AMD to aflibercept are substantially diminished after increasing treatment intervals from 4 to 8 weeks. *Acta Ophthalmol*, 93, e510-1.


