Thesis

Anti-vascular endothelial growth factors treatment of wet age-related macular degeneration: from neurophysiology to cost-effectiveness

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List of the original publications

This dissertation is based on the following original publications, which will be referred to in the text by their Roman numerals:


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### List of abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>ANCHOR</td>
<td>Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal neovascularization</td>
</tr>
<tr>
<td>AMD</td>
<td>Age-related macular degeneration</td>
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<tr>
<td>Anti-VEGF</td>
<td>Anti-vascular endothelial growth factor</td>
</tr>
<tr>
<td>BCVA</td>
<td>Best corrected visual acuity</td>
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<tr>
<td>BM</td>
<td>Bruch's membrane</td>
</tr>
<tr>
<td>CATT</td>
<td>Comparison of Age-related macular degeneration Treatments Trials</td>
</tr>
<tr>
<td>CEA</td>
<td>Cost-effectiveness analysis</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CNV</td>
<td>Choroidal neovascularization</td>
</tr>
<tr>
<td>CUA</td>
<td>Cost-utility analysis</td>
</tr>
<tr>
<td>DMI</td>
<td>Juvenile diabetes</td>
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<tr>
<td>DRN</td>
<td>Deviance-related negativity</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>EOG</td>
<td>Electro-oculography</td>
</tr>
<tr>
<td>ERG</td>
<td>Electoretinogram</td>
</tr>
<tr>
<td>ERP</td>
<td>Event related potential</td>
</tr>
<tr>
<td>ETDRS</td>
<td>Early treatment in diabetic retinopathy study</td>
</tr>
<tr>
<td>FAG</td>
<td>Fluorescein angiography</td>
</tr>
<tr>
<td>fERG</td>
<td>Flash electroretinogram</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
</tr>
<tr>
<td>GA</td>
<td>Geographic atrophy</td>
</tr>
<tr>
<td>HORIZON</td>
<td>Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration</td>
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<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
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<td>HTA</td>
<td>Health technology assessment</td>
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<tr>
<td>ICER</td>
<td>Incremental cost effectiveness ratio</td>
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<td>ICG</td>
<td>Indocyanine green angiography</td>
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<td>ILM</td>
<td>Inner limiting membrane</td>
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<tr>
<td>IPL</td>
<td>Inner plexiform layer of retina</td>
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<tr>
<td>IVAN</td>
<td>Inhibition of VEGF in Age-related Choroidal Neovascularisation</td>
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<tr>
<td>LogMAR VA</td>
<td>Logarithmic minimum angle of resolution visual acuity</td>
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<tr>
<td>MARINA</td>
<td>Minimally Classic/Occult Trial of the anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD</td>
</tr>
<tr>
<td>MEG</td>
<td>Magnetoencephalography</td>
</tr>
<tr>
<td>mfERG</td>
<td>Multifocal electroretinogram</td>
</tr>
<tr>
<td>mfVEP</td>
<td>Multifocal visual evoked potential</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NEIVFQ</td>
<td>National Eye Institute Visual Functioning Questionnaire</td>
</tr>
<tr>
<td>OCT</td>
<td>Optical coherence tomography</td>
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<tr>
<td>OPL</td>
<td>Outer plexiform layer of retina</td>
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<tr>
<td>PDT</td>
<td>Photodynamic therapy</td>
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<tr>
<td>PERG</td>
<td>Pattern electroretinogram</td>
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<tr>
<td>PED</td>
<td>Pigment epithelium detachment</td>
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<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>PRN</td>
<td>Pro re nata</td>
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<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
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<tr>
<td>RGC</td>
<td>Retinal ganglion cells</td>
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<tr>
<td>RPE</td>
<td>Retinal pigment epithelium</td>
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<tr>
<td>SD OCT</td>
<td>Spectral-domain optical coherence tomography</td>
</tr>
<tr>
<td>SEVEN UP</td>
<td>Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials</td>
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<tr>
<td>TD OCT</td>
<td>Time-domain optical coherence tomography</td>
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<tr>
<td>TER</td>
<td>Treat-and-extend regimen</td>
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<tr>
<td>VA</td>
<td>Visual acuity</td>
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<tr>
<td>VECP</td>
<td>Visually evoked cortical potential</td>
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<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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<tr>
<td>VEOG</td>
<td>Vertical electro-oculogram activity</td>
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<tr>
<td>VEP</td>
<td>Visual evoked potential</td>
</tr>
<tr>
<td>VER</td>
<td>Visual evoked response</td>
</tr>
<tr>
<td>WTP</td>
<td>Willingness to pay</td>
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Kuopio, September 2016

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Abstract

Wet age-related macular degeneration (AMD) is the leading cause of blindness in the elderly in the Western world, causing suffering to the individual and high social and healthcare costs to society. During the last decade, anti-vascular endothelial growth factors (anti-VEGF) have become the first choice treatments for this previously devastating condition. Currently, there are three intravitreally injected anti-VEGF medications available: bevacizumab, ranibizumab and aflibercept. Clinical trials have shown that these three anti-VEGF medications exert similar effects on visual acuity and possess similar safety profiles, although aflibercept requires less frequent injections. In fact, the required frequency of repeated injections represents a major burden on ophthalmology clinics.

Visual evoked potential (VEP) recording offers a non-invasive tool to investigate the function of the visual pathway. The aims of this study were to determine (1) how the VEP changes after bevacizumab injections, (2) if VEP is useful as a diagnostic or monitoring tool for wet AMD, (3) if the binocular face detection task improve after anti-VEGF injections, and (4) which anti-VEGF medication and injection protocol may be considered as most cost-effective.

The publication I was a pilot study of six wet AMD-patients treated with anti-VEGF injections, where VEP revealed that its latency had shortened and amplitude increased after the treatment. The subsequent publications II and III were non-randomized cohort studies. A total of 16 patients with unilateral wet AMD and six healthy control subjects were included. The patients received three bevacizumab injections every 4 weeks after the last injection with a similar time interval used for the non-treated controls. In publication II, significant changes (p < 0.05) were found in the following parameters in the treated eyes: logMAR visual acuity decreased on average by 0.18 ± 0.32 units, optical coherence tomography (OCT) retinal thickness decreased by 170 ± 200 μm and VEP amplitude increased by 1.0 ± 1.4 μV. There was a significant correlation between the relative changes of VEP amplitude and retinal thickness r = −0.630 (p < 0.05), and between visual acuity (logMAR) and retinal thickness r = 0.576 (p < 0.05). These results seem to indicate that the application of VEP does not confer any additional benefits in the diagnosis or monitoring of wet AMD.

In publication III, face pictures elicited well-defined event-related components in occipital and parieto-occipital cortical areas at baseline and after treatment. The face-specific N170 component was pronounced in all subjects with longer peak latency in patients than in controls (p = 0.032). However patients did not experience any significant improvement in face-specific electrical potentials after the anti-VEGF treatment.

In publication IV, the cost-effectiveness of the three anti-VEGF injections and two injection protocols (i.e. regular monthly and pro re nata) for wet AMD were compared. A two-eye Markov transition model was developed for this analysis and a result reinforced by the sensitivity analyses.

National Library of Medicine Classification: W 74, WW 103, WW 166, WW 270
Medical Subject Headings: Wet Macular degeneration/drug therapy; Neurophysiology; Drug Costs; Treatment Outcome

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Silmänpohjan kostean ikärappeuman hoito anti-VEGF injektiolla: neurofysiologiasta kustannusvaikuttautuvuuteen
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Tiivistelmä


Näköheräyvästä (VEP) on ei-kajoava menetelmä, jolla tutkitaan näköradan toimintaa. Tämän väitöskirjaturutkimuksen tavoitteena oli (1) selvittää kuinka VEP muuttuu injektiohoitojen seurauksena, (2) tutkia voidaanko VEP:ää käyttää silmänpohjan kosteaa ikärappeuma diagnosoinnissa tai seurannassa, (3) selvittää muuntuuko kasvojentunnistustehtävän heräytä hoidon myötä ja (4) tunnistaa mikä anti-VEGF lääkeaineista ja kahdesta hoitoprotokollasta (säännöllinen, työläiskäyttö tai tarvitteessa annosteltava) on kustannusvaikutuvaikkaikärappeuman hoitovaihtoehtoja.

Pilottitutkimuksessa I todettiin, että VEP:issä läsnä lyhentyi ja amplitudin kasvoi hoidon myötä. Ei-satunnaistetuissa kohortitutkimuksissa II ja III oli 16 yhden silmän kosteaa ikärappeuma sairastavaa potilasta ja kuusi tervettaa kontrollia. Potilaat saivat kolme bevasitsumabii-injektiota 4-6 viikon välein. VEP tehtiin injektiosarjaa ennen ja 4-6 viikoa viimeisen
injection jälkeen. Kontrollipotilailla käytettiin vastaavaa tutkimusväliä. Tutkimuksessa II todettiin tilastollisesti merkittävä muutos (p < 0.05) seuraavissa muuttuajissa: logMAR näöntarkkuus parantui −0.18 ± 0.32 yksikköä, retinian paksuus ohentui 170 ± 200 µm ja VEP:n amplitudi kasvoi 1.0 ± 1.4 µV. Tilastollisesti merkittävä korrelatio (p < 0.05) todettiin VEP amplitudin suhteellisen muutoksen ja verkkokalvon paksuuden muutoksen välillä r = −0.630 sekä näöntarkkuuden (logMAR) ja verkkokalvon paksuuden muutosten väliillä r = 0.576. Näiden tulosten perusteella VEP ei vaikuta tuovan lisähoidon sairauden diagnoosinnassa tai seurannassa.


Tutkimuksessa IV selvittiin eri verisuonikasvutekijä estäjä yhteydessä ja seurannasta. Tätä varten kehitettiin kahden silmin Markovin tilansäätymällä ja tehtiin sensitiivisyysanalyysit mallin parametreille. Säännöllinen kuukausittainen beavatisümästi todettiin kustannusvaikutavimmaksi hoitovaihtoehdoksi.

Luokitus: W 74, WW 103, WW 166, WW 270

Yleinen suomalainen asiasanasto: silmänpohjan ikärappeuma, lääkehoito, neurofysiologia, kustannustehokkuus

Introduction

Age-related maculopathy (AMD) is a degenerative disease of the central retina called the macula (Arnold & Heriot 2007). This area of retina is responsible for gathering detailed visual information from the environment such as that needed for reading a newspaper or recognizing a face. The prevalence of AMD is clearly related to age. In a pooled analysis of population-based data, the prevalence of AMD in the population aged 55–64 was 0.2% whereas in the population older than 85 years it had risen to 13% (Smith et al. 2001). AMD can have severe effects on an individual’s life and it is the leading global cause of irreversible blindness (Mitchell et al. 1995; Klein et al. 1999; Fine et al. 2000; Klaver et al. 2001; Gehrs et al. 2006; Wong et al. 2008; Kawasaki et al. 2010). It has been estimated that AMD causes 8.7% of all blindness globally, and the number of cases is predicted to increase from 196 million in 2020 to 288 million by 2040 (Wong et al. 2014).

There are two forms of AMD; these are called wet (i.e. neovascular or exudative) and dry (i.e. nonexudative) AMD (Bird et al. 1995). In general, AMD is characterized by drusen formation and pigment changes in the choroid and retinal pigment epithelial (RPE) layers in the macula (de Jong 2006; Jager et al. 2008). In wet AMD, new vessels develop from the pre-existing vasculature in a process called angiogenesis or neovascularization. Vascular endothelial growth factors (VEGF) are the most important factors in this retinal and choroidal neovascularization, leading to oedema, haemorrhages and in the late stage, also fibrosis and ultimately visual impairment (Kinnunen & Ylä-Herttuala 2012a; Rofagha et al. 2013).

Wet AMD is diagnosed in 10–15% of the patients with AMD. Both forms can lead to legally-defined blindness as defined by the World Health Organization, although wet AMD was responsible for 80% of these cases before the arrival of the novel treatments for wet AMD (Ferris et al. 1984; Ojamo 2015). Typically, the treatment of wet AMD is started when the patient is elderly, on average 77 years of age (Brown et al. 2006; Rosenfeld et al. 2006; CATT Research Group et al. 2011).

The two forms of AMD can be distinguished from each other by clinical examination, optical coherence tomography (OCT) and fluorescein angiography (FAG) (Yonekawa et al. 2015). With FAG, the diagnosis can be confirmed. With OCT, the retinal thickness can be measured, and thus this parameter can be used as a monitoring tool to assess the response to treatment with the wet AMD (Bajwa et al. 2015).

Intravitreal anti-VEGF injections, which were introduced a decade ago, have revolutionized the treatment of wet AMD (Solomon et al. 2014). These agents have been demonstrated to reduce or even terminate the neovascularization and thereafter decrease the intraretinal oedema and improve visual acuity (VA; Schmidt-Erfurth et al. 2014a). Currently there are three anti-VEGF injections available: aflibercept, bevacinumab and ranibizumab. They have been shown to have similar effects and safety profiles, but they differ from each other in terms of price and injection interval (CATT Research Group et al. 2011; Schmidt-Erfurth et al. 2014b).

The intravitreal injections need to be administered at regular intervals and therefore this is a clear disadvantage demanding considerable healthcare resources and in some rare cases causing adverse ocular events (Cruess et al. 2007; Amouak et al. 2015). There are many large-scale clinical trials of wet AMD patients above 65-years of age demonstrating the retinal structural changes and VA improvement achieved after anti-VEGF injection (Rosenfeld et al. 2006; Abraham et al. 2010; CATT Research Group et al. 2011, IVAN Study Investigators et al. 2012, Ho et al. 2014; Schmidt-Erfurth et al. 2014b), but there are no publications of neurophysiological changes after anti-VEGF injections in older patients (i.e. subjects above 65 years of age) suffering from wet AMD.

The visual evoked potential (VEP) is a non-invasive neurophysiological examination evaluating the function of the visual pathway from the retina via the optic nerves to the visual cortex of the brain (Nyrike & Pääkkönen 2006). VEPs are electrical potentials elicited by visual stimuli, which are recorded from the scalp on top of the visual cortex and extracted from the electro-encephalogram (EEG) by signal averaging. VEP has been shown to be more sensitive in the diagnosis of optic neuritis than imaging techniques such as magnetic resonance imaging (Ko 2010). VEP recording with binocular face stimuli simulates in a standardized clinical setting, the everyday situation of face detection.

The treatment of wet AMD patients is resource consuming and it is responsible for a major economic strain on the healthcare budget (Cruess et al. 2008). From the perspective of society, the treatment should be reserved for those individuals who will gain the most benefit, in view of the high costs of the treatment. For wet AMD, there
are a few medications with different treatment schedules available. This has triggered the need to compare these treatment strategies to ensure that society as a whole is benefitting. Cost-effectiveness analysis can be used to compare these different treatment options by examining the costs against the change of quality adjusted life years (QALY; Räsänen & Sintonen 2013). In practice, this is done by applying simplified models such as a Markov transition model (Drummond et al. 2005). However, until this present study, there were no two-eye models comparing all three intravitreal injections and their possible treatment regimens with lifelong treatment period.

The purpose of the publications I–III was to evaluate the changes of VEP after the anti-VEGF injections and to investigate how the VEP parameters would be correlated with clinical findings. Our aim was to study whether VEP could be used as a diagnostic or monitoring tool for these patients. In a binocular face detection task, we simulated the everyday situation of face perception with the aim of detecting changes in this attribute after the anti-VEGF injections. In the publication IV, we constructed a two-eye Markov transition model to simulate the binocular situation of ordinary patients and used this model in the cost-effectiveness analysis of wet AMD treatment.

Review of the Literature

Anatomy of the visual pathway

The visual pathway is a part of nervous system, starting from the retina of the eye, propagating via the optic nerves and tract, and terminating at the visual cortex of the brain (see Fig. 1; Nyrke & Pääkkönen 2006). The optical structures of the eyes, including cornea and ocular lens as well as the light-transparent structures including anterior chamber and vitreous, can influence the handling of the light signals received by the retina, but are not considered to be part of the visual pathway.

Retina

The retina is about a 0.5 mm thick lining at the back of the eye, which is composed of three layers of nerve cell bodies and two layers of synapses (see Figs 2 and 3; Kolb 1995). The outer nuclear layer contains cell bodies of the photoreceptors, the rod and cone cells, which are located next to the pigment epithelium and the choroid. The inner nuclear cell layer contains the cell bodies of the bipolar, horizontal and amacrine cells. The ganglion cell layer contains the cell bodies of ganglion cells and some amacrine cells. These three nerve cell layers are separated by outer (OPL) and inner plexiform layers (IPL). In the OPL, there are connections between rods and cones, and the vertically oriented bipolar cells and horizontally located horizontal cells. In the IPL, there are connections between the bipolar cells and the horizontal cells. The amacrine cells both influence and integrate their actions with the ganglion cells and in that way they can influence the signal. The central retina is cone-dominated whereas the peripheral retina is rod-dominated. The fovea is located in the middle of the macula area on the temporal side of the optic nerve head. In this area, the cones are concentrated at their maximum density and there are no rods. The ganglion cell axons are located in the nerve fiber layer toward the optic nerve head in an arcuate pattern (Hoon et al. 2014).

The retina receives its blood supply from the central retina artery and choroidal blood vessels. The choroidal blood supply is especially important for the maintenance of the outer retina including the photoreceptors (Kur et al. 2012).
The light must travel through the retina before it can activate the rods and the cones (Kolb 1995). The rods are exquisitely sensitive to light, being responsible for dim-light vision whereas cones are sensitive to specific wavelengths of light. Subsequently, the photoreceptors absorb the photons and further convert the resulting biochemical message into an electrical message, which is then conveyed as a graded potential through the succeeding layers of the retina. The final retinal message is transmitted to the brain as action potentials as the spiking discharge patterns of the ganglion cells (Hoon et al. 2014).

**Optic nerve and optic tract**

The axons from the retinal ganglion cells (RGC) form the retinal nerve fiber layer; they converge in the optic nerve head (Oster & Sretavan 2003). The optic nerve head is composed of the nerve fiber layer, the prelaminar region, the lamina cribrosa and the retrolaminar region. After passing through lamina cribrosa, the optic nerve is myelinated by oligodendrocytes. The two optic nerves converge at the optic chiasm, where the nerve fibers originating in the nasal retina of each eye intersect to become combined with the temporal fibers of the fellow eye (see Fig. 1). In the lateral geniculate nucleus, the RGC axons synapse with next neurons. Only 5–10% of the synapses in the lateral geniculate nucleus originate from RCG, in fact the majority arise from reciprocal or feedback connections from the thalamic reticular nucleus, pulvinar nucleus, and the visual cortex. Most of the fibers from the optic tract synapse in the lateral geniculate nucleus, while a minority connect to the superior colliculus, a brain region which plays a role in the control of saccadic eye movements, visual orientation, eye-tracking and binocular vision. The axons of the following neurons continue to the visual cortex through the optic radiations (de Moraes 2013).

**Central nervous system of vision**

The axons of the optic radiation neurons synapse in the primary visual cortex known as VI or Brodmann area 17 (de Moraes 2013). In humans, most of the primary visual cortex is located in fissures and only the macular projection area extends to the posterior surface of the occipital pole although there is extensive inter-individual variation. The central ten degrees of the visual field cover at least 60% of the occipital cortex. Visual information then passes to secondary visual areas known as V2, V3, V4 and V5 (Wandell et al. 2007; Burnat 2015).

After reaching the visual cortex, stimuli from the retina need processing before they can be perceived as images (Melcher & Morrone 2015). Multiple areas of the brain are involved in this complex simultaneous cascade, which even today is partially unresolved. As the information passes through the visual system, the complexity of the neural representations increases, for example, while V1 neurons respond to a single line, neurons in the lateral occipital complex respond to an object and neurons in the visual association cortex respond to human faces (Kaas et al. 2015; Melcher & Morrone 2015; Peirce 2015).

**Evaluation of the function of the visual pathway**

There are a number of ways in which one can examine the visual pathway or its component parts, starting from the retina and ending in the visual cortex. Some of these techniques focus on anatomical or structural imaging and some on the evaluation of the function of the visual pathway.

**Clinical examination**

**Visual acuity.** The basic parameter and starting point of every ophthalmic examination is the measurement of visual acuity (VA) in the patient; this depends on the optical and neural factors, and therefore gives only a glimpse of the function of visual pathway (Kalloniatis & Luu 1995a). VA may be assessed as being normal even if there is a major defect in the visual field e.g. caused by a stroke and on the other hand, VA can be impaired due to optic opacities such as cataract, even though the visual pathway is intact. There are a number of charts, based on characters of different sizes and specified viewing distances, to measure and express VA such as Snellen VA, logarithmic minimum angle of resolution (LogMAR) VA and the early treatment in diabetic retinopathy study (ETDRS) letter score. These generally used VA measurements are interchangeable (Holladay 1997; Shamir et al. 2016). Visual acuity is affected by refractive error, illumination, contrast and the location of the retina under stimulation (Kalloniatis & Luu 1995a).

**Contrast sensitivity, color vision and visual fields.** There are a few alternative ways to test contrast sensitivity including Pelli-Robson chart, which can detect pathological changes in visual function even when VA is normal (Trobe et al. 1996). Color vision is usually tested with Ishihara’s pseudoisochromatic plates. To categorize congenital dyschromatopsias, then the Farnsworth D-15, Lanthony desaturated D-15 and Farnsworth-Munsell 100-hue or its subset consisting of chips 22–42 can be used. Acquired color sensitivity is reduced in inflammatory, infiltrative and compressive optic and chiasmal neuropathies, whereas in macular diseases, the color sensitivity is less disturbed than the VA (Kalloniatis & Luu 1995b).

Visual field defects caused by lesions in the retina, optic nerve, chiasm and visual pathways generate a limited set of defect patterns providing the clinician with an approximation of the localization of the lesion (Kedar et al. 2011). Further examinations are needed to identify the lesion.

**Amsler grid.** The Amsler grid is a grid of horizontal and vertical lines, which can be used as a patient self-monitoring method to detect macular disturbances. The patients are looking at the Amsler grid monocularly and try to detect possible scotomas or distortions of the lines. The sensitivity of the Amsler grid for the detection of new onset wet AMD seems to be quite low in comparison to fluorescein angiography (FAG; Do et al. 2012).

**Imaging techniques**

**Fundus photography, fluorescein angiography and indocyanine green angiography.** Color fundus photography can be used in the diagnosis and grading of AMD (Bird et al. 1995). Autofluorescence imaging of the fundus can reveal drusens as a hyper-reflection of lipofuscin accumulation and the geographic atrophy (GA; i.e. large area of pigment epithelium loss) as a severely reduced signal (Holz et al. 2015). The fundus photographs are simple and quick to perform unless optical opacities exist in the eye.

The FAG is the golden standard for diagnosing and classifying the wet AMD (Arnold & Heriot 2007). Therefore, it is routinely recommended, but contraindicated if there has been a previous anaphylactic reaction to
Fluorescein (Schmidt-Erfurth et al. 2014a). FAG can be used in the assessment of the classification of the subtype of wet AMD, but it seems to be challenging since the classification varies considerably between retina specialists even in repeated observations by the same observer (Holz et al. 2003; Zayit-Soudry et al. 2007).

Indocyanine green angiography (ICGA) can be used in the diagnosis, if one cannot make the diagnosis based on the FAG. Specifically, it can reveal polypoidal choroidal vasculopathy (Schmidt-Erfurth et al. 2014a). In the case of severe drusen formation, ICGA can reveal the occult choroidal neovascularization (CNV) not observed by FAG (Landa et al. 2007).

**Optical coherence tomography.** Optical coherence tomography (OCT) is useful in revealing the anatomical structures of the macula (see Fig. 3). It is a non-invasive cross-sectional imaging technique, quick to perform and it produces objective and reproducible quantitative measurements of retinal thickness and volume of the macula (Hunter et al. 2013). Therefore it can be used in the diagnosis and monitoring of wet AMD. The technical development of OCT has been relatively fast and accuracy has increased. In comparison to FAG, OCT is shown to have sensitivity of 94% and specificity of 89% in detecting new CNV lesion (Bajwa et al. 2015).

Since the inception of the OCT and its application of the ocular analysis, the diagnostics and monitoring of retinal diseases have changed dramatically (Huang et al. 1991). Time-domain OCT (TD-OCT) was introduced in year 2002 for commercial use and a few years later, spectral-domain OCT (SD-OCT) entered the market. TD-OCT and SD-OCT use a different imaging technique, i.e. SD-OCT has greater resolution and a much shorter acquisition time. It seems that image assessments of macula with SD and TD-OCT are reasonably well comparable, even though SD-OCT is believed to be superior in the detection of disease activity. The active lesions were detected with TD-OCT in 71.8% of the cases in comparison to SD-OCT in 87.1% of the cases (p < 0.001) (Major et al. 2014). SD-OCT detects fluid about 5% more frequently than TD OCT due to TD OCT’s lower resolution and artifactual interpretation of dark areas as cystoid oedema (Folgar et al. 2014).

Spectral-domain OCT (SD-OCT) has high sensitivity for detecting choroidal neovascularization (CNV), but its specificity is rather low (80.8%) when compared to FAG (100%) (Wilde et al. 2015). In a meta-analysis of OCT, the pooled values for sensitivity and specificity in detecting wet AMD were 85% (95% confidence interval (CI), 72–93%) and 48% (95% CI, 30–67%) (Castillo et al. 2015). Based on these results, the diagnosis of wet AMD should not solely be based on OCT.

In clinical trials of wet AMD, the measurement of retinal thickness has been based on OCT (e.g. Rosenfeld et al. 2006; Catt Research Group et al. 2011, Ivan Study Investigators et al. 2012, Ho et al. 2014; Schmidt-Erfurth et al. 2014b). Since the different OCT systems use different retinal segmentation algorithms leading to differences in the retinal thickness measurements, the outcomes are not necessarily directly comparable (Wolf-Schnurrbusch et al. 2009). There is no expert consensus on which anatomical structures should be included in the assessment of retinal thickness.

Recently, OCT has been claimed to be an option to performing autofluorescence-based imaging and angiography (Spaide et al. 2015a). Angiography OCT is a novel retinal vasculature imaging technique not entailing any dye injection but still capable of visualizing the retinal vasculature and abnormal blood flow, although the technique’s artefacts can lead to incorrect interpretation (Spaide et al. 2015a, b; Morgan 2016). In clinical practice, the use of these options is still relatively rare and the methods still need development before they will replace FAG in the diagnosis of wet AMD (Gong et al. 2016).

Computed tomography and magnetic resonance imaging in visual pathway research. The traditional methods of structural brain imaging, computed tomography (CT) and magnetic resonance imaging (MRI), provide limited information about the visual tracts (Prasad 2014). MRI should include fat-suppressed T1 and T2-weighted sequences in order to identify the enhancement of optic tract. CT can identify fractures of the orbit or skull base, orbital mass lesions, abnormalities in the extraocular muscles and calcifications. CT can also be used when MRI is contraindicated (Prasad 2014). Functional MRI is a method for visualizing the activation of brain areas by detecting increased or decreased blood flow after interventions (Phillips et al. 2012).

**Visual evoked potential and other neurophysiological methods**

**Visual evoked potential.** The visual evoked potential (VEP), also known as the visual evoked response (VER) or the visually evoked cortical potential (VECP) refers to electrical potentials elicited by visual stimuli (Nyrk & Pääkkönen 2006). They are recorded from the scalp overlying the visual cortex. The VEP waveforms are extracted from the EEG by applying a signal averaging method. For example, VEPs can be used to measure the functional integrity of the visual pathways and all the abnormalities influencing on the visual pathway or visual cortex can affect the VEP responses (Creed 1995; Odom et al. 2016). The pattern VEP responses in the visual cortex originate mainly from the stimulation of the macula (i.e. the central visual field) and depend on functional integrity of the central vision of the pathway (Odom et al. 2016).

In the 1930s, it was noticed that a strobe flash initiated VEPs in the raw EEG (Odom et al. 2016). Any evoked potential, such as auditory, somatosensory or visual signals, can be extracted from the EEG by signal averaging. Today this can be easily done with amplifiers and computer software. Signal averaging refers to the procedure of repeating the stimulus and collecting the time-locked electrical responses and then calculating the mean signal at each time point. In this way, the random EEG activity (i.e. noise) is averaged out, leaving only the VEP (Nyrk & Pääkkönen 2006; Odom et al. 2016).

The visual evoked potentials can be recorded at various scalp locations in humans since any visual stimulus evokes activity both in the primary visual cortices, secondary cortices and a number of tertiary brain regions (Melcher & Morrone 2015; Odom et al. 2016). In clinical practice, VEPs are usually recorded from the occipital scalp regions overlying the calcarine fissure, which is the closest location to
the primary visual cortex (i.e. the Brodmann’s area 17). A generally accepted and standardized system for placing the electrodes is the “10–20 International System”, which is based on the measurements of the head size (Jasper & Rasmussen 1958). It uses six standard electrodes know as O1, O2, T5, T6, Pz and Oz. The electrode Oz is placed on the midline in the occipital region at a distance above the inion calculated as 10% of the distance between the inion and nasion, which in most adults is 3–4 cm. The inion refers to the most prominent projection of the occipital bone at the posterior-inferior part of the skull and the nasion is the bridge of the nose between the eyes. The electrode Pz is placed 20% above the Oz. The lateral occipital electrodes O1 and O2 are placed at a similar distance from the midline, and electrodes T5 and T6 are placed more laterally (Odorn et al. 2016).

Most of the electrical potentials are generated in sulci and simultaneously at multiple locations (Towle et al. 1995; Slotnick et al. 1999). In addition, there is vertical cancellation between upper and lower visual fields. The neural generators of VEP waves are not easy to clearly specify. One interpretation is that visual cortex is the source of the early components of VEP N1 (N75) before P1 (P100) (Slotnick et al. 1999). The early phase of the P1 component which has a positive peak around 95–110 milliseconds is likely generated in dorsal extrastriatal cortex of the middle occipital gyrus. The following negative component N2 (N150) is generated from multiple areas, including a deep source in the parietal lobe (di Russo et al. 2002). In the occipital area, the brain activity varies considerably. Numerous dipolar fields are generated, resulting in a complicated interaction (Towle et al. 1995), making source localization challenging at the individual level.

When performing a VEP recording, the scalp locations need to be prepared in order to minimize contact impedance (Odorn et al. 2016). A reference electrode is placed on the forehead and a ground electrode can be placed on mastoid or scalp. The room lighting and distance to the stimuli should be standardized. Each eye is analysed separately and any refractive error has to be corrected. After the onset of the stimulus, the time period to be analyzed is usually between 200 and 500 milliseconds. The amplifier bandpass limits are commonly 1 and 100 Hz. There are a variety of standardized test protocols, such as strobe flash, transient and steady pattern reversal and pattern onset/offset stimuli each developed for specific purposes. The checkerboard pattern is the most commonly applied stimulus in clinical practice; this reverses every second or half-second and is displayed by a video monitor (see Fig. 4). With pattern reversal stimuli, individuals generally produce similar evoked potential as shown in Fig. 5. At a peak time of 75 milliseconds, there is a negative peak called N1 or N75, at about 100 milliseconds there is a positive peak called P1 or P100 and about 135 milliseconds there is a negative peak termed N2 or N135. Differences in the stimulus parameters influence the VEP and therefore each laboratory needs to have their own reference data (Odorn et al. 2016).

When using the half-field VEP, only the right or left visual field receives the stimulus. It can be used to detect lesions located posterior to the chiasm, where as whole field VEP is used primary to detect pre-chiasmal lesions (Chiappa & Hill 1997).

The amplitudes (i.e. height of the peak) and the latencies (i.e. the time from stimulus onset to the peak) are measured from the VEP waveforms (Odorn et al. 2016). Furthermore, the configuration of VEP can be analyzed visually. The components of VEP change gradually with age exhibiting an attenuation in amplitude and slowing of the P1 component (Emmerson-Hanover et al. 1994). In some cases, VEP is more useful than imaging techniques, for example it has been shown that VEP is more sensitive for detecting opticus neuritis than MR imaging (Ko et al. 2010).

**Fig. 4.** Checkerboard pattern with red fixation point.

**Multifocal VEP.** Traditional VEP evaluates the whole retina, the optic nerves and central pathway as a single unit, whereas in multifocal VEP (mfVEP), the responses are recorded simultaneously over multiple regions of the visual field (Hood et al. 2003). By using mfVEP, one can isolate smaller dysfunctional areas by using hundreds of simultaneous stimulations without summing abnormal and normal responses. The reversing check pattern can be used as the stimulus. mfVEP can be used as an objective topographic assessment of the visual field (Young et al. 2012).

**Electroretinogram.** The electroretinogram (ERG) is a mass electrical response of the retina to photic stimulation and it can be used to assess the status of the retina and especially the photoreceptors (France 1984). It is based on the electrical activity of the retina induced by standard flash light stimulus (flash ERG, fERG) and the voltage difference between the cornea and retina. The recording electrodes are placed on the cornea, bulbar conjunctiva or skin on the lower lid. The reference electrode is typically placed on the forehead. The clinical examination starts with dilation of the pupils and 30 min dark adaptation followed by six responses based on the light adaptation state of the eye and the strength of the flash: (1) rod ERG, (2) combined rod-cone fERG, (3) dark-adapted 3 oscillatory potentials reflecting photoreceptor function, (4) dark adapted strong flash ERG analysing the function of amacrines cells, (5) light adapted ERG measuring cone and bipolar cell function, and (6) light-adapted 30 Hz flicker ERG sensitive to cone function. From these ERG responses a-waves, b-waves and the latencies of the first four oscillating potentials are measured (McCulloch et al. 2015). In clinical practise fERG can be used to diagnose various retinal diseases causing dysfunction of retinal cells such as retinitis pigmentosa and cone dystrophies (Iarossi et al. 2003; Langwieska-Wosko et al. 2015). At fERG can also be used to analyse the visual function of infants (France 1984).

The multifocal electroretinogram (mfERG) provides a topographic assessment of the health or dysfunction of the macula (Hood et al. 2012). It might be useful for example in the
detection and follow-up chloroquine induced maculopathy (Halfeld Furtado de Mendonca et al. 2007). The pattern ERG (PERG) is the response obtained by stimulation of the central retina by reversing black and white checkerboard. The PERG allows a direct measure of ganglion cell function (Holder 2001).

**Electro-oculography.** The electro-oculography (EOG) is the study of retinal function in resting electric potentials of the eye. This potential is mainly derived from RPE. EOG measures the standing potential in the dark and in the light. Usually this is expressed as a ratio of the maximum amplitude in the light and the minimum amplitude in the dark. Often there is a correlation between EOG and ERG, but for example in Best vitelliform maculopathy ERG is normal and EOG can be highly abnormal (Marmor et al. 2011).

**Face detection and recognition**

Face recognition and the ability to identify facial expressions are fundamental aspects of human social interactions (Little et al. 2011). Face detection (i.e. perception) and subsequent face recognition (i.e. identification) are complex tasks involving mainly three bilateral regions of the brain: inferior occipital gyrus, superior temporal sulcus and lateral fusiform gyrus (Haxby et al. 2000). The face recognition capability starts to develop during the first months of life (Heron-Delaney et al. 2011). Failure to receive visual stimulus during this time period, for example due to congenital cataract leads to permanent deficits in face identification tasks (le Grand et al. 2001, 2003; Mondloch et al. 2013). At the other end of the life cycle, one of the first reported symptoms detected in AMD patients is an impairment in face recognition, leading to difficulties in social interactions (Bullimore et al. 1991).

It has been debated whether a face is a specific stimulus to the brain; for example, brain lesion studies have revealed an inability to recognize faces and expression, although other objects can still be correctly identified (Kanwisher et al. 1997; Calder & Young 2005; Barnes et al. 2011). This situation, where a person cannot recognize faces due to a brain lesion, is known as prosopagnosia. Furthermore, there is a case report of a patient who was unable to identify general objects, but had retained the ability to recognize faces (Moscovitch et al. 1997). Brain imaging with electrophysiological approaches e.g. electroencephalography (EEG), event related potential (ERP), magnetoencephalography (MEG) and metabolic examinations (e.g. positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)) offer tools to clarify these face detection and recognition mechanisms (Labar et al. 2003; Fairhall & Ishai 2007; Dekowska et al. 2008; Tsao & Livingstone 2008). For instance, if one records the VEP, it is evident that a sudden face stimulus elicits a face specific configuration peak at approximately 170 milliseconds; this is named N170 and can be prominently observed over the visual cortex. When N170 is elicited by a face stimulus in comparison to non-face object, it is larger in amplitude, often peaks a few milliseconds earlier and displays a more consistent right hemisphere lateralization (Rossion 2014).

**Age-related macular degeneration**

Age-related related macular degeneration (AMD) is a bilateral ocular condition that affects the macula and is the leading cause of blindness in the elderly in the Western world (Javitt et al. 2003; Klein et al. 2004; Cruess et al. 2007; Jager et al. 2008). In the United States of America, the prevalence of AMD among people above 60-years of age is 13.4% and prevalence of severe AMD is 0.8% (Klein et al. 2011). The prevalence of AMD is clearly age related. A population based pooled data revealed that AMD was present in 0.2% of individuals aged 55–64 years, but this had risen to 13% of the population older than 85 years (Smith et al. 2001). The presence of AMD exerts a major impact on the physical and mental health of the geriatric population and their families. Individuals with AMD suffer from loss of central vision leading to an inability to read a newspaper, to drive a car and to recognize familiar faces. Furthermore, AMD increases the risk of suffering depression or hip fractures (Ivers et al. 2003; Anastasopoulos et al. 2006; Wysong et al. 2009). The independence of these subjects is threatened and they may end up moving into institutional care. All of these factors cause severe loss of quality of life (Sahel et al. 2007; Soubrane et al. 2007; Matamoros et al. 2015). Without treatment, binocular wet AMD leads to severe blindness in a 5 year period in about 50% of cases (Macular Photocoagulation Study Group 1993). In recent data from Finland, AMD was responsible for 42% of all cases of legal blindness (7507 people) and 59% of all incidents of legal blindness above 65 years of age (Ojamo 2015).

**Etiology and risk factors**

Age is the primary risk factor for wet AMD (Mitchell et al. 2002; Javitt et al. 2003; Klein et al. 2004; Mukesh et al. 2004; Cruess et al. 2007; Jager et al. 2008). Other risk factors include smoking, positive family history, female gender, obesity, high blood pressure, atherosclerosis and hypercholesterolemia (Age-Related Eye Disease Study Research Group 2000, Klein et al. 2004, 2008; Buch et al. 2005; Katta et al. 2009). Quitting smoking will diminish the risk, but the risk remains elevated even after...
20 years (Klein et al. 2014; Zerbib et al. 2014).

The development and presentation of AMD is at least partially hereditary (Fritsche et al. 2013, 2016). There seems to be some ethnic differences, i.e. the prevalence of AMD is higher in Europeans than in Asians or Africans (Wong et al. 2014).

Pathophysiology
The pathophysiology of AMD is a topic of intense research, but all the details of this complex phenomenon are far from clear. No clear-cut initiation of the progression of dry AMD into the wet AMD form has been identified (Klettner et al. 2013; Kauppinen et al. 2016).

Biochemical, histological and genetic studies have indicated several pathways involved in the pathogenesis of AMD (Kauppinen et al. 2016). Typically AMD starts with the dry form with drusens and/or pigment disruption, representing the basis for the early clinical diagnosis. The drusens are deposits that lie between the RPE and basement membrane also known as Bruch’s membrane (BM) and they can trigger inflammation in the surrounding tissues via a complex molecular cascade. In addition to drusens, there are also basal laminar deposits and basal linear deposits, which also are suspected to play a role in the development of AMD (Gemenetzii & Lotery 2014; Kauppinen et al. 2016).

From a histopathologic point of view, the earliest manifestation associated with AMD is encountered at the interface of macular retina and the underlying layer of the choroid consisting blood vessels and connective tissue (Sarks et al. 1999; Sarraf et al. 1999). This is the site containing photoreceptors, RPE cells, BM, and the choriocapillaris. It is believed that RPE and BM form a barrier, limiting the cellular migration, especially the invasion of neovascular tissue from the choroid into the subretinal space. The molecular changes occurring in BM are not fully understood, but they do seem to involve changes of homeostasis that are due to the inflammation around drusens. When the RPE interface to the BM is disrupted by this inflammatory process, the blood vessels from the choroid can grow into this space (Wang & Hartnett 2016).

When RPE is degenerating in the macula, it also causes a dysfunction and degeneration of photoreceptors and has therefore an impact on central vision (Ferrington et al. 2016). It has been proposed that the source of RPE dysfunction is caused by a number of cellular risk factors, such as oxidative stress, inflammation, protein aggregation and attenuating autophagy (Klettner et al. 2013; Ferrington et al. 2016). In addition, choriocapillaris can have a role in the process of AMD (McLeod et al. 2002). In certain cases, vascular endothelial growth factors (VEGF) may be upregulated leading to the development of AMD. VEGF-A plays a key role in this process (Otrock et al. 2007).

The structural changes caused by wet AMD take place in the retina and in the cortex since there is some evidence for cortical plasticity after various ophthalmic problems (Martins Rosa et al. 2013). There is no published evidence that wet AMD would cause a deterioration or any harm to the optic nerve.

Clinical presentation and diagnostics of AMD
Clinically, AMD can be classified into the dry and the wet forms (see Fig. 6) (Bird et al. 1995). Wet AMD is less common; only accounting for about 10–15% of cases of AMD, but before the development of anti-VEGF treatment, it caused about 80% of the cases of legal blindness (Sunness 1999). In dry AMD, drusens and pigmented changes are present. The dry AMD can progress into wet AMD, which can lead to the formation of a disciform scar if left untreated. This process takes several months resulting in a geographic atrophy (GA) with RPE loss and a thinning of the retina (Holz et al. 2014).

AMD affects both eyes, but the symptoms and findings may be asymmetric (Solomon et al. 2014). The development of wet AMD may affect one eye or both eyes simultaneously or sequentially. Patients with wet AMD in one eye have a 40% risk of developing the disease also in the other eye over a period of 5 years. During the early stages of AMD, the patients may be asymptomatic, but in late stages, AMD causes metamorphopsia (distortion of objects), scotomas and blurry vision. Many subjects might be unaware of the monocular symptoms unless tested specifically. Already in the early stages of AMD, contrast sensitivity, visual adaptation, colour discrimination, the rate of recovery after photostress and dark adaptation deteriorate, and central visual field defects may occur (Owsley et al. 2001, 2006; Jackson

Fig. 6. On the top row, (A) OCT and (B) fundus photograph of left eye of a patient with dry AMD. The arrows indicate drusens. On the bottom row, (C) OCT and (D) fundus photograph of left eye of a patient with wet AMD. In picture C, the arrow indicates intraretinal oedema and in picture D, the arrow indicates hemorrhage.
et al. 2004; Neelam et al. 2009). The amplitude and latency of foveal retinogram (ERG) response decline due to the disruption to the function of photoreceptors (Li et al. 2001).

Age-related macular degeneration is defined by fundus examination, but the diagnosis of AMD is typically based on age, clinical findings, OCT, fundus autofluorescence, FAG and/or ICG (Kaarniranta et al. 2016). The designation of wet AMD implies that fluid, exudates and/or blood are present in the extracellular space between the neural retina and the RPE (i.e. subretinal space) and/or in the case of RPE, there is a detachment of the RPE from Bruch’s membrane (i.e. the sub-RPE space) (Kaarniranta et al. 2011, 2013; Kinnunen et al. 2012). In wet AMD, a choroidal neovascular membrane (CNV) is present; this originates from the normal choriocapillaris and extends through a dehiscence in Bruch’s membrane (BM) into the subretinal or sub-RPE space. Sometimes multiple soft drusen form confluent areas, creating large pigment epithelium detachments (PED), which are elevations of RPE under the retina (Wang & Hartnett 2016).

Currently, there are several standardized systems for classification and grading the severity of AMD to assist the researchers and clinicians in the diagnosis and management of this disease, but none of these have achieved global use. In clinical research used systems include for example the Wisconsin age-related maculopathy grading system, the international classification for age-related macular degeneration and the Clinical Age-Related Maculopathy Staging system (Klein et al. 1991; Bird et al. 1995; Seddon et al. 2006). The so-called standardized classification system of AMD is often used in epidemiologic studies and is based on the presence and size of the area covered by hypopigmentation, hyperpigmentation, drusen, geographic atrophy (GA) and/or the presence of CNV. Based on these evaluations AMD can be classified as early AMD with drusen and RPE pigmented abnormalities or late AMD, which includes dry AMD with the presence of GA and late AMD with the presence of RPE detachment, hemorrhages and/or scars (Bird et al. 1995). However, more precise grading systems are also available (Ferris et al. 2013). Wet AMD can be divided into subtypes of classic, predominantly classic, minimally classic, occult wet AMD and disciform scar based on FAG findings of dye leakage (Jung et al. 2014).

Depending on the stage of the AMD, there are various macular dystrophies and other ocular conditions mimicking AMD (Saksens et al. 2014). Early stages with drusens have to be distinguished from flecks, which are typically attributable to hereditary macular conditions such as fundus flavimaculatus (i.e. Stargardt’s disease) or different vitelliform lesions. Similar findings to GA can be displayed by macular dystrophies causing choriretinal atrophy such as Sorsby fundus dystrophy and North Carolina macular dystrophy. Choroidal neovascularization (CNV) can also be present, for example in Sorsby disease, pattern dystrophies, dystrophies with angioid streaks and parafoveal telangiectasias. In central serous chorioretinopathy, there can be atrophic lesions accompanied by yellow subretinal deposits and even CNV mimicking different stages of AMD (Gass & Oyakawa 1982; Saksens et al. 2014). Other reasons for CNV include myopic degeneration, ocular inflammation, ocular infections and trauma (Rouvas et al. 2011; Adatia et al. 2015; Díaz et al. 2015). Nowadays, polypoidal neovascularization is often seen as a subtype of wet AMD; this is more commonly encountered among the Asian population (Wong et al. 2016).

**Treatment**

Two decades ago the diagnosis of wet AMD was devastating for the patient. Photodynamic therapy (PDT), in which intravenously administered verteporfin (Visudyne®, Novartis Pharma GmbH, Nuremberg, Germany) is activated by laser, was the only available treatment with a rather dubious efficacy (Wu & Murphy 1999). Ten years ago, the development of frequent intravitreal anti-VEGF injections revolutionized the treatment and these novel agents have shown superiority in the visual outcome in comparison to PDT (Kaiser et al. 2007). Nowadays, PDT is used primarily in specific cases of nonresponders to anti-VEGF treatment (Amoakou et al. 2015).

**Anti-VEGF injections.** Pegaptanib (Macugen®, Pfizer Manufacturing Belgium NV, Puurs, Belgium) was the first commercially available anti-VEGF injection registered in 2004, but soon ranibizumab (Lucentis®, Novartis Pharma GmbH, Nuremberg, Germany) achieved clinically better responses (Gragoudas et al. 2004; Solomon et al. 2014). In addition, low priced bevacizumab (Avastin®, Roche Pharma AG, Grenzach-Wyhlen, Germany) has been used as an off-label medication when it is administered intravitreally. The use of off-label intravitreal bevacizumab has triggered an intense political debate in many countries (Lotery & MacEwen 2014). Recently in Finland, the Council for Choices of Health Care working under the Ministry of Social Affairs and Health has stated that bevacizumab intracocularly should be included in the publicly funded choices for intracocular treatment of wet AMD in Finland (Ministry of Social Affairs and Health 2015). The latest anti-VEGF is aflibercept (Eylea®, Bayer Pharma AG, Berlin, Germany) with the benefit of a longer injection interval and equivalent efficacy as ranibizumab (Thomas et al. 2013; Schmidt-Erfurth et al. 2014b).

The aim of anti-VEGF is to inhibit the angiogenesis mediated by VEGF and most often its isomer VEGF-A (Senger et al. 1983). In humans, in addition to VEGF-A there are also VEGF-B, -C, -D and placental growth factor participating in this process (Maglione et al. 1991; Olofsson et al. 1996; Joukov et al. 1997; Achen et al. 1998). The pegaptanib is a 28-nucleotide RNA aptamer of 50 kDa with a high selectivity for the VEGF-A isoform. Aptamers are chemically synthesized molecules with high specificities and affinities. Bevacizumab is a full-length humanized monoclonal IgG antibody of 149 kDa inhibiting all VEGF-A isoforms. Ranibizumab is an engineered recombinant humanized Fab fragment of 48 kDa designed from the full-length monoclonal antibody bevacizumab in order to optimize retinal penetration. Ranibizumab binds with high affinity to a site present in all VEGF-A isoforms and their bioactive proteolytic fragments. Aflibercept is a fully human recombinant protein of 115 kDa. It consists of key binding domains from the VEGF receptor-1 and 2 fused to an IgG Fc fragment. It acts as a soluble decoy receptor recognizing and neutralizing all VEGF-A isoforms and unlike the other anti-VEGFs in use, aflibercept inhibits also...

Treatment protocols for anti-VEGF injections. The optimal treatment of wet AMD should start immediately or within a few days after the diagnosis to achieve the best improvement in best corrected visual acuity (BCVA) (Rasmussen et al. 2015). There are three treatment protocols. First, the regular or fixed monthly injection protocol, where the injection is given regularly without clinical assessment. In the case of aflibercept, after administering three monthly loading injections, the agent is administered every second month. Second, the pro re nata (PRN) protocol, where the injection is given based on clinical findings or other indications such as OCT findings. Third, the treat-and-extend regimen (TER) where the control and injection intervals are extended after inactive disease is achieved (Spaide 2007). With 6 months’ follow-up, it seems that three loading injections of bevacizumab achieve a better VA than the PRN protocol from the start of therapy (Arias et al. 2008). Thereafter, clinically in the short term, bevacizumab and ranibizumab with the regular monthly injections and PRN protocol after three loading injections seem to be equally effective in improving and sustaining the VA (Busbee et al. 2013; Jiang et al. 2014). When monthly injected bevacizumab or ranibizumab have been compared to PRN treatment, it has been claimed that there might be a higher risk of developing geographic atrophy (GA) but there appear to be no differences with scar formation (Daniel et al. 2014; Grunwald et al. 2014). GA growth is dependent on several ocular factors, and there is one report that ranibizumab might accelerate GA growth in comparison to bevacizumab (Grunwald et al. 2015). So far, TER has not been evaluated in any prospective randomized controlled clinical trials. A systematic review suggested the superiority of TER to PRN (Chin-Yee et al. 2015). Furthermore, groups of retina specialists have stated that TER seems to be an effective approach in the individual wet AMD treatment (Freund et al. 2015).

After the three loading injections, aflibercept is administered every second month without reducing beneficial anatomical or VA effect (Nguyen et al. 2012). Ranibizumab injected monthly compared to aflibercept injected every second month seems to have an equivalent effect on VA and quality of life (Schmidt-Erfurth et al. 2014b; Yuzawa et al. 2015). In conclusion, the more frequent and patients’ time consuming injections do not seem to lower the quality of life.

Long-term results. In the two-years’ follow-up clinical trials of different anti-VEGF injections, VA improved and retinal thickness decreased (Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group et al. 2012, Waldstein et al. 2016). Subsequently, in five to seven years’ follow-up, the visual acuity was not sustained, but nonetheless, the advantages of the treatment were clear. It was also shown that despite stable chronic fluid detected with OCT, VA can be sustained and a dry macula may not be evidence of better VA (Rofagha et al. 2013; Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group et al. 2016). The long-term use of anti-VEGF injections might have some disadvantages. An in vitro study has indicated that anti-VEGF neutralizes the protective effect of VEGF in retinal ganglion cells (Brar et al. 2010) and furthermore, there is no in vivo study demonstrating that the long-term use of anti-VEGF injections is associated with reduction of ganglion cell layer thickness (Beck et al. 2016). There is lack of long-term real-life results of these treatments.

Adverse events. Intraocular injections pose a potential ocular risk (Schmid et al. 2015). These risks include endophthalmitis, uveitis, retinal detachments, retinal tear, vitreous hemorrhage and ocular-vessel occlusion or embolism. The risk of these adverse events is <1% during a 1 year follow-up. It seems that aflibercept, bevacizumab and ranibizumab have similar ocular side effects (Catt Research Group et al. 2011, Schmidt-Erfurth et al. 2014b). The risk of GA development is higher with monthly ranibizumab treatment compared to PRN bevacizumab treatment (Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group et al. 2012). A sustained increase in the intraocular pressure can occur in a range from 3.45% to 11.6% of patients (Dedania & Bakri 2015).

The risk of systemic side effects, including ischemic stroke, acute myocardial infarction, congestive heart failure and venous thromboembolism, of intravitreal injections of aflibercept, bevacizumab and ranibizumab seem to be very low and similar between the individual medications (Campbell et al. 2012; Moja et al. 2014; Wang & Zhang 2014; Schmid et al. 2015; Sarwar et al. 2016). Some meta-analysis of serious systemic adverse events favor ranibizumab over bevacizumab (Chen et al. 2015). In comparison to placebo, all three medications have increased the risks for serious side effects: aflibercept 2 mg 5.29% (95% confidence interval (CI) 3.18–7.39; p < 0.001), bevacizumab 1.25 mg 5.58% (95% CI 3.57–7.60; p < 0.001) and ranibizumab 0.5 mg 5.33% (95% CI 4.37–6.30; p < 0.001) (Schmid et al. 2015). However, a recent publication compared wet AMD patients before anti-VEGF treatment existed and anti-VEGF treated patients, and found no elevated risk of myocardial infarction, stroke and death in the anti-VEGF treated patients (Yashkin et al. 2016).

Treatment of dry AMD. There is no cure available for dry AMD (Schmid et al. 2015). It has been shown that high-dose supplementation of vitamins C and E, beta carotene and zinc, can reduce the risk of AMD progression by 25–30% over a 5 year period. Since beta carotene can be associated with lung cancer, it can be substituted by lutein and zeaxanthin in this formulation (Age-Related Eye Disease Study Research Group 2001, Age-Related Eye Disease Study 2 Research Group 2013). Ongoing clinical trials of dry AMD are focusing on elucidating the mechanisms causing the disease such as inhibiting the complement pathway, reducing oxidative stress, inhibiting lipofuscin formation and enhancing regeneration of RPE cells from the stem cells, but to date, no curative treatment is available (Hanus et al. 2016).

Blindness due to wet AMD

Age-related macular degeneration is the leading cause of legal blindness (Snellen equivalent VA <0.3) in the Western world and the third most common reason in global terms causing significant societal costs (Cruss et al. 2008; Bourne et al. 2013). In the prevention of blindness, the anti-VEGF treatment has been successful. In Denmark, the number of legally blind persons due to AMD was halved.
after the introduction of anti-VEGF therapy (Bloch et al. 2012). In addition to direct problems caused by blindness, the low VA is associated with the Charles Bonnet syndrome (Lampela et al. 2005). This syndrome is thought to be caused by the deprivation of visual stimuli. It is characterized by visual hallucinations occurring in psychologically normal patients and can be very distressing for the patient (Singh & Sorensen 2012).

**Influence of intravitreal anti-VEGF treatment on the visual pathway of wet AMD patients**

The starting point of the visual pathway, i.e. the retina, has been in major focus of interest of AMD research. Numerous clinical trials have demonstrated the significant benefit of this therapy in reducing retinal thickness and the VA increase has also been frequently reported in wet AMD patients receiving anti-VEGF treatment (Rosenfeld et al. 2006; Abraham et al. 2010; Catt Research Group et al. 2011, Ivan Study Investigators et al. 2012, Ho et al. 2014; Schmidt-Erfurth et al. 2014b). At the cortical level of the brain, the systemic side effects and adverse events of the anti-VEGF injections are established and the likelihood of stroke with different anti-VEGF medications are: bevacizumab 0.9%, ranibizumab 1.1% and aflibercept 0.5–0.8% (Rosenfeld et al. 2006; Heier et al. 2012; Moja et al. 2014). However, a recent study states that there is no increase of strokes due to anti-VEGF injection (Yashkin et al. 2016).

In general, the effects of macular diseases on the function of visual pathway evaluated by VEP have been recognized (Marcus et al. 1983; Folk et al. 1984; Bass et al. 1985; Sherman et al. 1986; Johnson et al. 1987; Kato et al. 1991; Shimada et al. 1997; Sabeti et al. 2013), but in these studies the changes after the possible treatment have rarely been reported. It seems that macular diseases mainly delay the latencies and have less influence on the reduction in the amplitude. For instance, Kato et al. (1991) reported minor modulation in macular hole patients with only a reduction in amplitude but no change in the latencies. This indicates that VEP delays cannot distinguish macular disease from optic nerve disease if other tests are not performed. In studies involving multifocal stimulation (mfVEP) conducted adult in diabetic subjects with or without retinopathy there was evidence of a significantly delayed VEP in comparison to nondiabetic controls. The mfVEP amplitude measurement appeared to be less sensitive to the effects of diabetes than the latency measurement. Furthermore, a specific analysis of mfVEP indicated that zones with retinopathy showed significantly delayed VEP compared to zones without retinopathy (Wolff et al. 2010). In a study conducted in children with type I diabetes, VEP revealed that amplitude values decreased, and latency values increased progressively with the years (Karlica et al. 2010). In the study of Pai et al. (2007), 21 vein occlusion patients were successfully treated with bevacizumab injection and VEPs were measured in two patients before injection and at 4 weeks without any changes in VEP.

There are only very few studies where patients have been treated for wet AMD and the possible neurophysiological changes followed (Liu et al. 2009; Macky & Mahgoub 2012). A safety study of intravitreal bevacizumab detected no changes on ERG or VEP in rabbits after one injection (Shahar et al. 2006). Macky & Mahgoub (2012) examined a young population (mean age 50 years, range 24–62 years) with 32 AMD and 23 myopic patients treated with one bevacizumab injection. During the 6 weeks’ follow up, no statistically significant changes were found in the amplitude or latency of the VEP waves or in the ERG A and B-waves. They observed a statistically significant improvement in the photopic B-wave of the injected and fellow eye. Due to the very young age of that population, the reliability of their AMD diagnosis can be questioned. Liu et al. (2009) studied mfERG and VEP changes after combination therapy with PDT and intravitreal bevacizumab. They reported that this treatment could increase the response amplitudes of mfERG in follow-up which took place 6 months after drug injection.

The recovery of the nervous system after any kind of injury takes a relatively long period of time; for example the recovery of optic neuritis takes 2–6 months (Wilhelm & Schabet 2015). A number of different types of nerve injuries occur followed by complex cellular and molecular peripheral and central degeneration and regeneration, and in specific cases cerebral reorganization, but these processes are beyond the focus of this thesis.

**Cost-effectiveness of wet AMD treatment**

**Cost-effectiveness in health economics**

One needs to apply protocols from economics if one wishes to evaluate the efficiency of resource utilization (Begg et al. 1997). The Pareto efficiency refers to the case when it is impossible to make one person better off without making at least one person worse off. One important model in economics is the concept of perfect competition since it leads to Pareto efficient resource allocation (Drummond et al. 2005). In health economics, the aim is somewhat modified: resources should be distributed so that efficiency and equality are achieved, and further the health of the population should be maximized. Here, efficiency refers to the maximization of health with the given resources and the desired health level is achieved with a minimum amount of resources (Sintonen & Pekurinen 2006). When one wishes to assess the benefits of some medication or health care equipment, then an evaluation process called health technology assessment (HTA) can be applied (Mäkelä & Lampe 2007).

There are several ways of conducting an HTA but all of them take costs into account. Depending on the chosen perspective, there are variations in the particular costs that need to be taken into account. The costs can be divided into the following categories with examples: direct health care costs (medication and instruments), direct non-health care costs (homecare services and travel costs), indirect costs (working hours lost due to the disease) and time costs (patients’ time spent at the health care unit). In different HTA options, the costs of the treatments are measured according to the perspective, but major differences will arise depending on which method is applied for measuring the health effect. In one of these methods, the cost-effectiveness analysis (CEA), the change in costs is compared to change in the health effect, which is measured in natural units such as life years gained or change in blood pressure. Cost-utility analysis (CUA) is a special case of CEA, since it uses quality-adjusted life years (QALY) gained as the unit of effect. This method provides the
opportunity to compare the treatments of different medical fields (Drummond et al. 2005). The HTA is recommended to be performed from a societal perspective, but other perspectives such as the hospital or patient perspective can also be applied (Martikainen et al. 2006).

The result options of CEA are summarized in Fig. 7 (Briggs & Gray 1999). The old therapy is in the origin and the horizontal and vertical axes represent the difference between the two therapy methods. In quadrants I and III, the result is not necessarily obvious and therefore the incremental cost effectiveness ratio (ICER) can be assessed. The ICER measures the change in costs in relation to change in effects and it can be calculated from the formula

\[
\text{ICER} = \frac{C_n - C_o}{E_n - E_o}
\]

where \( C \) = cost, \( E \) = effect, \( n \) = new treatment, \( o \) = old treatment (Martikainen et al. 2006). In the Fig. 7 the gray line represents the willingness to pay (WTP) frontier, i.e. on the left hand side is the area, where the society is willing to adopt the new treatment method, in other words, it is, willing to pay some extra cost to achieve better health (Briggs & Gray 1999).

The ICER can be calculated from clinical studies that are usually randomized, controlled clinical trials (Martikainen et al. 2006). In addition, an analytical model including a decision tree or a Markov transition model can be used. The Markov transition model can be used to analyse the cost-effectiveness of two or more treatment options of chronic diseases with different health states called Markov states combined with respective different utilities and healthcare costs (see Fig. 8). The duration of the time horizon analyzed and the length of cycles (i.e. the length of time in a certain health state) have to be chosen depending on the disease and intervention being evaluated. The transition probabilities from one health state to another and the starting health state have to be identified usually based on longitudinal cohort studies. A patient can be only in one health state at one time. Therefore, in Fig. 8 \( p_1 + p_3 + p_5 = 1 \) and \( p_2 + p_4 + p_6 = 1 \) and \( p_7 = 1 \), where \( p_n \) is the transition probability. In the model, one can assume a cohort of 1000 or one patient to enter, but in the end, the number of patients is irrelevant. From this data, the total cost of the treatment and total units of utility accumulated can be calculated, and thereafter one can estimate the cost of one utility unit gained. The Markov transition model is a stochastic process, where the new health state is only dependent on the previous health state without a memory from earlier health states (Briggs & Sculpher 1998; Drummond et al. 2005).

The HTA is generally done based on clinical trials (Martikainen et al. 2006), which might not correspond to the everyday clinical effect. Furthermore, the models are always a simplification of the often very complex reality since they may not take into account some important details. Therefore it is generally recommended that one should also perform a sensitivity analysis of the model parameters (Drummond et al. 2005).

Costs and QALYs of AMD treatment
Frequent injections are often needed to stabilize the condition of a patient with wet AMD (Catt Research Group et al. 2011, Schmidt-Erfurth et al. 2014b). In Finland, with its increasing number of elderly people, this means that the total annual number of injections per year is increasing, leading to higher total costs (Tuulonen et al. 2009). There is a significant difference between the prices of the individual anti-VEGF preparations. For instance, the Kuopio University Hospital Disease Related Grouping -prices of a single injection of these medications in May 2016 were as follows: bevacizumab 70€, ranibizumab 909€ and aflibercept 718€. In the CEA, all the costs have to be taken into account according to the selected perspective. In the analysis, the future costs and outcomes are discounted and sometimes calculating the costs based on previously published prices will need to be corrected by applying a price index.

In health economics, the term utility refers to the satisfaction of needs or effect on well-being followed by resources utilization. A rational individual tries to maximize the utility. Efficiency means the relation between the resource input and the effect achieved with these inputs (Sintonen & Pekurinen 2006). This effect can be measured by health-related quality of life (HRQoL) by generic or disease-specific instruments. National Eye Institute Visual Functioning Questionnaire (NEIVFQ) represents a visual and eye disease specific instrument, which has been validated for AMD (Orr et al. 2011). These disease-specific instruments are suited for clinical evaluation of the treatment, whereas the generic instruments can be used to compare diverse patient groups and different diseases. The generic instruments can measure a profile describing the health state on

![Fig. 7. The cost-effectiveness plane showing the different result options of the analysis. Modified from Briggs & Gray (1999).](image)

![Fig. 8. Simplified Markov transition model.](image)
various dimensions or produce a single index score on a 0–1 scale, which is necessary if one wishes to calculate QALYs. The QALY’s advantage of measuring HRQoL is that it can simultaneously measure the change of quality and length of life (Räsänen et al. 2006). The QALY measurement must be conducted with a method, which is (1) based on preferences, (2) anchored between perfect health and death, and (3) measured on an interval scale (Drummond et al. 2005). One QALY signifies one year in a perfect health condition whereas a QALY value of zero represents death. The single index-score generic indicators include 15-dimensional health state descriptive questionnaire (15D), the EuroQol Group Association five domain questionnaire (EQ-5D), the Health Utility Index instrument 3 (HUI3) and the Short Form Health Survey (SF-6D) which make it possible to undertake a comparison between different fields of medicine (Sintonen 2013). The assessment of QALY should be based on the patient’s own experience, ideally in a before-after treatment setting and not only on the evaluation by healthcare professionals in order to avoid bias (Räsänen et al. 2006). Nonetheless, an individual’s capability of adapting to the prevailing health condition in some cases makes it difficult to measure QALY reliably (Dolan & Kahneman 2008).

A few studies of QALY of AMD patients using the generic instruments have been conducted in the United States of America, United Kingdom and Japan (Brown et al. 2000; Yanagi et al. 2011; Butt et al. 2013). The number of patients included in these studies has varied from 48 to 80. These works used various generic instruments and also direct methods of evaluation. In general, AMD patients have evaluated their QALY lower than the general population (Butt et al. 2013). In a comparison of VA and contrast sensitivity, it has been noted that improvement in contrast sensitivity shows a higher increase of QALY (Butt et al. 2014). In the diseases affecting the central vision, such as AMD, the VA of the better seeing eye correlates better with the HRQoL (Hirneiss 2014).

Cost-effectiveness of anti-VEGF treatment of wet AMD
Since healthcare resources are limited, a treatment needs to be cost-effective. The cost-effectiveness of anti-VEGF injections is dependent on the costs of treatment and on the QALYs accumulated. The treatment regimen, the injection interval or the medication used does not seem to exert a major influence on the accumulation of QALYs (Dakin et al. 2014; Schmidt-Erfurth et al. 2014b; Yuzawa et al. 2015). Therefore, the cost-effectiveness studies have used VA as an indicator of utility. In the case of eye disease, which affects both eyes, one can analyse the cost effectiveness of the treatment by taking into account one eye only (i.e. one-eye model) or both eyes (i.e. two-eye model).

There are numerous studies on cost-effectiveness of AMD treatment. It has been shown that PDT is more cost-effective than no treatment (Mitchell et al. 2011). Subsequently, ranibizumab and bevacizumab have been shown to be more cost-effective than PDT (Hodge et al. 2010). The dominance of bevacizumab over ranibizumab is apparently due to the high price difference (Canadian Agency for Drugs and Technologies in Health 2014). Bevacizumab PRN treatment seems to be more cost-effective than monthly injections (Stein et al. 2014).

Aflibercept, which requires less frequent injections, is a new treatment option but only a few cost-effectiveness studies have been conducted for this therapeutic agent (Elshout et al. 2014; Kourlaba et al. 2015; Murra Anton 2015; Tempelaar et al. 2015; Panchmatia et al. 2016). Elshout et al. (2014) used a two-eye model with a Monte Carlo simulation comparing the cost-effectiveness of aflibercept, bevacizumab and ranibizumab in the Netherlands. They used a 2–5 year time span and concluded that bevacizumab PRN was the most cost-effective treatment option followed by bevacizumab monthly, aflibercept, ranibizumab PRN and finally ranibizumab monthly. Murra Anton (2015) compared aflibercept and ranibizumab PRN in Mexico over a 2 years time span with a Markov model and stated that aflibercept was favoured. Kourlaba et al. (2015) used a one-eye Markov model comparing aflibercept with ranibizumab monthly and PRN a 20 year time horizon assuming that the treatment ended at the end of the second year. They concluded that aflibercept was the most cost-effective treatment. Tempelaar et al. (2015) compared aflibercept to ranibizumab monthly and PRN over a 15 year time horizon with an unspecified model assuming that the treatment ended at the end of second year. They also concluded that aflibercept would be the most cost-effective treatment. Panchmatia et al. (2016) compared aflibercept and ranibizumab in Sweden with a 2 years’ one-eye Markov model and concluded that aflibercept was the most cost-effective treatment option.

There are some concerns about the current cost-effectiveness analysis of AMD treatment. Most of the studies have been based on a one-eye model (e.g. Raftery et al. 2007; Hernandez-Pastor et al. 2008, 2010; Neubauer et al. 2010; Athanasakis et al. 2012). These one-eye models assume that the treated eye is the better seeing eye and the worse seeing eye does not receive any treatment which is not invariably the case. In addition, many of the studies have often been limited to time periods of 1–2 years (e.g. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group et al. 2012, Dakin et al. 2014). A model of chronic eye disease in which the VA of both eyes is impaired, such as is the case in AMD, can reflect the clinical practice, only if both eyes are incorporated into the model. Furthermore, with a chronic progressive disease such as wet AMD that needs sustained treatment, the time-horizon should cover the whole treatment period.

Aims of the Study
The general aim of this study was to evaluate the neurophysiological changes of wet AMD patients after the anti-VEGF treatment and to assess whether whole-field pattern VEP could be used as a monitoring tool of AMD patients. In addition, the cost-effectiveness of AMD treatment was evaluated.

The specific aims were as follows:

1 To identify the possible visual evoked potential changes after the anti-VEGF treatment (Publication I).
2 To evaluate if visual evoked potential changes correlate with clinical findings of treated patients (Publication II).
3 To study whether binocular face detection is affected by monocular wet AMD (Publication III).
4 To construct a two-eye Markov transition model for the cost-effective analysis of AMD treatment and to identify the most cost-effective treatment protocol and medication for wet AMD (Publication IV).
Changes in Neurophysiologic Markers of Visual Processing Following Beneficial Anti-VEGF Treatment in Macular Degeneration

Abstract

**Purpose:** Antivasular endothelial growth factor (VEGF) agents have been shown to improve visual acuity and prevent vision loss in exudative age-related macular degeneration. As the vision improves relatively quickly in response to intravitreal injections, we wanted to know whether this improvement is reflected in electrophysiological markers of visual cortical processing.

**Patients and methods:** Our interventional case series included six elderly patients who underwent injection treatment in the affected eye. Their visual acuity, tomographic images of retinal thickness, and visual evoked potentials (VEP) were assessed before treatment and six weeks after the last injection.

**Results:** All patients showed improved visual acuity and reduced retinal fluid after the treatment. All but one patient showed increased VEP P100 component amplitudes and/or shortened latencies in the treated eye. These VEP changes were consistent with improved vision while the untreated eyes showed no changes.

**Conclusions:** Our results indicate that antivasular endothelial growth factor injections improved visual function of the treated eyes both at the level of the retina and at the level of visual cortical processing.

**Keywords:** age-related eye diseases, exudative age-related macular degeneration, visual evoked potentials, scalp-recorded EEG, visual acuity

Introduction

Age-related macular degeneration (AMD) is the major cause of blindness in the elderly in Western countries. It is characterized by a progressive loss of color and fine vision, reduced contrast, and spatiotemporal sensitivity.

Clinically, AMD can be classified into early- or late-atrophic AMD (i.e., dry AMD), or exudative (i.e. wet) AMD (Gehrs et al. 2006). Wet AMD is characterized by a proliferation of choroidal neovascularization. Excessive expression of vascular endothelial growth factor (VEGF) by retinal pigment epithelial (RPE) cells leads to new vessel formation originating from the choroid and extending through defects in the Bruch’s membrane and the RPE sub-and intraretinally (Salminen et al. 2010). Vision loss occurs through the structural and metabolic damage in the retina and in the RPE cells (Gehrs et al. 2006; Salminen et al. 2010; Kaarniranta et al. 2011). To date, anti-VEGF (bevacizumab or ranibizumab) intravitreal injections have been shown to be an effective treatment to decrease retinal fluid in exudative AMD (Catt Research Group et al. 2011, Ivan Study Investigators et al. 2012). Vision improvement occurs within 1 month and continues to improve over the next few months.

Optical coherence tomography (OCT) is a standard technique for cross-sectional imaging of the retina. OCT is useful in quantitatively evaluating subretinal and intraretinal fluid, assessing any possible subfoveal involvement of neovascularization, and in monitoring anti-VEGF intravitreal injection response. Visual evoked potentials (VEP) provide quantitative information on the functional integrity of well-defined visual pathways in the central nervous system. For instance, for analysis of the visual pathways, VEP are considered more sensitive than magnetic resonance imaging in detecting optic neuritis and clinically silent lesions in multiple sclerosis (Ko 2010).

We aimed to investigate whether the improved vision by anti-VEGF treatment is reflected in the function of the visual pathways. Our hypothesis was that significant changes in VEP will be observed, and these changes may be related both to improvement in vision and decreased retinal fluid.

Materials and methods

The interventional case series consisted of six patients having exudative AMD. Diagnosis was based on the best corrected visual acuity (BCVA) testing, full biomicroscopy examination and OCT (Spectral OCT/SLO, Ophthalmic Technologies Inc, Toronto, ON, Canada) analysis in the Department of Ophthalmology, Kuopio University Hospital. For patient characteristics and their visual acuities see Table 1. At the first visit, when exudative AMD diagnosis was made, bevacizumab intravitreal injection was applied into the affected eye of each individual. The injection was performed three times, 6 weeks between injections. VEP, BCVA testing, full biomicroscopy analysis, and OCT examinations were performed at the first visit prior to anti-VEGF injection and 6 weeks after the last (i.e. third) injection, about 18 weeks after the first visit. The Ethics Committee of the Kuopio University Hospital had approved the study, and the tenets of the Declaration of Helsinki were followed. All participants provided informed consent.

<table>
<thead>
<tr>
<th>Patient</th>
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<th>Age</th>
<th>BCVA treated eye</th>
<th>BVCA non-treated eye</th>
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<td>P1</td>
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<td>P2</td>
<td>M</td>
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<td>P3</td>
<td>F</td>
<td>74</td>
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<td>P6</td>
<td>M</td>
<td>79</td>
<td>0.2</td>
<td>0.4</td>
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BCVA = best corrected visual acuity (Snellen equivalents), F = female, M = male, P = patient number.
Visual evoked potentials were recorded using a 64-channel electrode cap (EASYCAP GmbH, Falk-Minow Services, Ammersee, Germany) with the SynAmps2 amplifier (NeuroScan, Inc, El Paso, TX, USA). All scalp electrodes were referred to a midline centrofrontal electrode (FCz). Potentials reflecting eye blinks and vertical eye movements were recorded between electrodes placed above and below the right eye. All electrode impedances were kept below 10 kΩ. Signals were amplified and filtered with a bandpass of 0.1–50 Hz and digitized continuously at 500 Hz.

Pattern reversal VEP were elicited by a high contrast black and white checkerboard stimulus on a computer monitor using STIM2 software (NeuroScan, Inc). To cover the macular area with the stimulus, a circular stimulus field with a diameter of 10.3 degrees was used. The check size was 35 min of arc. The pattern was reversed at 1 Hz. A small red fixation target was positioned at two check widths above the center of the pattern stimulus. The viewing distance was 100 cm. Stimulation was monocular after occlusion of the other eye. For each eye and each recording session, responses to two blocks of 120 stimuli were recorded, with an undilated pupil under full refractive correction. Each patient’s individual images of optical coherence tomography are shown in Fig. 9. For one of the patients (P6), the primarily atrophic AMD changed to exudative form in the left eye during the study period (Fig. 9). This exudative form correlated well with decreased visual acuity and increased retinal thickness (Fig. 9 and Table 1). Note that anti-VEGF therapy had only a partial improvement for P3 and P6, in whom the reduction in retinal thickness observed in OCT was moderate (Fig. 9 and Table 2).

Retinal thickness (µm) was measured in individual patients with optical coherence tomography before and after injection in the treated and non-treated eyes. The VEP data were processed offline with SCAN software (NeuroScan, Inc). First, the continuous data from two recording blocks were merged into one file. Then the data were filtered (high pass 1 Hz) and segmented to epochs of 350 mseconds including a prestimulus interval of 50 mseconds. Epochs containing blinks or other artifacts were manually rejected. The artifact-free epochs were then averaged separately for each eye and each recording session. In averaging, both the mean and standard deviation were calculated on a point-by-point basis. Responses at electrode Oz were chosen for further analysis.

To test the statistical significance of the changes in VEP between the pre- to post-treatment recordings in each patient, Student’s t-test was applied to each time point of the VEP waveform. The level of statistical significance was set at p < 0.05. To reduce the probability of interpreting chance fluctuations as true changes, we set an additional requirement for a significant change: the probability level had to be <0.05 at least in four consecutive data points or at least over 8 mseconds.

Results

All patients showed improved vision in BCVA after the bevacizumab intravitreal treatment period (Table 1). This was in line with decreased retinal fluid (Fig. 9 and Table 2). Each patient’s individual images of optical coherence tomography are shown in Fig. 9. For one of the patients (P6), the primarily atrophic AMD changed to exudative form in the left eye during the study period (Fig. 9). This exudative form correlated well with decreased visual acuity and increased retinal thickness (Fig. 9 and Table 1). Note that anti-VEGF therapy had only a partial improvement for P3 and P6, in whom the reduction in retinal thickness observed in OCT was moderate (Fig. 9 and Table 2).

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Table 2. Retinal thickness (µm) in individual patients measured with optical coherence tomography (OCT) before and after injection in the treated and non-treated eyes.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treated eye</th>
<th>Non-treated eye</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before injection</td>
<td>After injection</td>
</tr>
<tr>
<td>P1</td>
<td>536</td>
<td>240</td>
</tr>
<tr>
<td>P2</td>
<td>330</td>
<td>240</td>
</tr>
<tr>
<td>P3</td>
<td>510</td>
<td>430</td>
</tr>
<tr>
<td>P4</td>
<td>440</td>
<td>240</td>
</tr>
<tr>
<td>P5</td>
<td>400</td>
<td>230</td>
</tr>
<tr>
<td>P6</td>
<td>420</td>
<td>263</td>
</tr>
</tbody>
</table>

P = patient number.
nontreated eyes. In five out of the six patients, post-treatment VEP waveforms indicated statistically significant changes compared to pretreatment waveforms, and these changes were consistent with improved vision in the treated eye. The VEP of the treated and untreated eyes of each patient before and after anti-VEGF treatment are illustrated in Fig. 10. The changes observed in P100 were decreases in latency and/or increases in amplitude. The time periods of the significant changes in the P100 component, which are consistent with improved vision, are marked with dark grey bars. All these changes were observed in the treated eye. Additional time periods with significant changes were observed outside the target component P100, and they are marked with transparent bars (Fig. 10). Those VEP changes were observed mainly in the eyes in which the treatment effect on P100 was significant, indicating that the whole VEP waveform may be affected. Slowing and/or reduced P100 amplitude was observed in the untreated eye in four out of six cases. The overall result in VEP is illustrated in Fig. 11, where the grand averaged waveforms of all six patients in the Oz scalp location are shown. Remarkably, the latency decrease was in the order of 7 milliseconds, and the amplitude increase in the order of 30% was observed at 18 weeks in elderly patients.

Discussion

Intravitreal injection of bevacizumab appears to achieve significant improvements in visual acuity and a reduction of retinal thickness secondary to exudative AMD (Rosenfeld et al. 2006; Catt Research Group et al. 2011, Ivan Study Investigators et al. 2012). The present results are in line with those of multicenter trials on the effect of bevacizumab in the treatment of exudative AMD. No ocular toxicity or adverse effects were observed in our patients for short-term bevacizumab treatment. Bevacizumab is well tolerated, as was shown in the previous large studies (Rosenfeld et al. 2006; Catt Research Group et al. 2011, Ivan Study Investigators et al. 2012). It is not known why some patients do not respond fully to anti-VEGF therapy. In the present study, the cases, P3 and P6 showed, only a limited response to bevacizumab. AMD is a multifactorial disease that affects the aging process of the RPE cells and their adjacent tissues, and this may play a role in the individual response to treatment (Kaarniranta et al. 2011). In addition, the delay to receive intravitreal anti-VEGF injection during active exudative AMD process may diminish treatment results (Rosenfeld et al. 2006). That may be the reason behind the results for cases P3 and P6.

A remarkable decrease in P100 latency and increase in amplitude was observed in the treated eye, but no changes were observed in the untreated eye in the VEP study. The changes in the VEP are most likely due to changes at

![Fig. 10. VEP in the Oz-FCz derivation before (thin line) and after (thick line) anti-VEGF treatment from the treated and nontreated eyes of six patients. Notes: The waveforms are the average of the about 240 sweeps presented in the two trials. The bars indicate the time ranges over which the curves differ statistically at the probability level of p < 0.05 at least over 8 mseconds. The dark grey bars correspond to changes consistent with improved vision (i.e., with a decrease in P100 latency and/or an increase in P100 amplitude), whereas the light bars correspond to opposite changes. The white bars correspond to changes outside the P100 component. In 5/6 patients, statistically significant changes consistent with improved vision in the treated eye were observed. Note that in P6, there had been a deterioration of vision in the untreated eye between the recordings leading to large changes in VEP from that eye. Abbreviations: VEP = visual evoked potentials, P = patient number.]
The Best-Corrected Visual Acuity and Retinal Thickness are Associated with Improved Cortical Visual Processing in Treated Wet AMD Patients

Abstract

Purpose: In response to anti-VEGF treatment for wet AMD retinal anatomy and visual acuity is often remedied. In our previous study, we showed that visual evoked potentials (VEP) improve following successful anti-VEGF treatment. The aim of the present study was to investigate how visual acuity and retinal thickness changes are reflected in VEP parameters. Moreover, we wanted to assess the feasibility of VEP as a novel monitoring tool for wet AMD patients.

Methods: 16 patients and six control subjects were enrolled in this study. Patients received three bevacizumab intravitreal injections. At the beginning of the study and four to six weeks after the last injection, the best corrected visual acuity (BCVA) test, full biomicroscope examination, OCT analysis and VEP were performed.

Results: In treated eyes, logMAR visual acuity decreased on average by 0.18 ± 0.32 units, OCT retinal thickness decreased by 170 ± 200 μm and VEP amplitude increased by 1.0 ± 1.4 μV. All changes were significant at p < 0.05. There was a significant correlation between the relative changes of VEP amplitude and retinal thickness r = −0.630 (p < 0.05), and between visual acuity (logMAR) and retinal thickness r = 0.576 (p < 0.05).

The macular level. However, if there were no processing changes at all in the higher levels of the visual system, one would expect that in those cases in which a large part of the macula stayed intact, there would be no delay in the onset of the P100 component. Our results (Fig. 2. Patients 1, 2, 3 and 6) show otherwise. Therefore we suggest that the changes in VEP are secondary to changes in the macula. We do however say that VEP is a neurophysiological marker of visual processing. Until now, the effects of intravitreal treatment of AMD in cortical visual processing are largely unknown. In one study of 21 vein occlusion patients successfully treated with bevacizumab injections, VEP were measured only in two patients before injection and at 4 weeks without any significant changes in VEP (Pai et al. 2007). However, a few reports of the possible changes in the function of visual pathways in diabetes do exist. A VEP study using multifocal stimulation (mfVEP) in adult subjects with diabetes showed significantly delayed VEP compared to nondiabetic controls (Wolff et al. 2010). Diabetic subjects with or without retinopathy demonstrated this delay. This suggests that retinopathy-free patients are showing early neurodegenerative changes occurring either at the level of the retina or upstream in the visual pathway that contribute to a cortical visual response. The mfVEP amplitude measurement appeared to be less sensitive to the effects of diabetes than the latency measurement. Furthermore, a specific analysis of mfVEP indicated that zones with retinopathy showed significantly delayed VEP compared to zones without retinopathy according to Wolff et al. (2010). Even in patients without retinopathy, the mfVEP is able to detect preclinical microvascular and/or neurodegenerative changes within or upstream from the retina. Recently a VEP study was also performed in 45 children, 15 with recently discovered juvenile diabetes (DMI), 15 children with long-lasting DMI, and 15 healthy children. Amplitude values decreased progressively, and latency values increased progressively in children with DMI as the years passed (Karlica et al. 2010).

Thus VEP can detect early signs of diminishing visual ability; however, we were able to detect encouraging VEP modulation within 18 weeks in our elderly patients who received intravitreal treatment for AMD. In this study, in most treated eyes, the latencies of P100 were shortened. Since the VEP is covering the whole area of the macula (the healthy part and not only the AMD affected area), the changes of P100 latencies were surprisingly long. One could assume that the healthy part of the macula would produce the signals with normal latencies, and only the affected area would produce longer P100 latencies. It also seems that signals from the healthy part are delayed. This can be interpreted in a way that suggests that there are changes in the visual pathway, and not only in the retina, despite the improved vision. Since no VEP changes toward the same direction were observed in the nontreated eye, the finding supports the concept that improved peripheral input plays a significant role in the neural plasticity of the visual cortex. In order to confirm these findings, larger population studies are required, and functional technological analyses are needed (Liu et al. 2009; Macky & Mahgoub 2012).

Acknowledgements

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Disclosure

The authors report no conflicts of interest in this work.
Conclusion: We showed that both the increase in VEP amplitude and the improvement in visual acuity are associated with the decrease in retinal thickness in treated wet AMD patients. The results do not indicate additional usefulness of VEP in the diagnosis or monitoring of wet AMD.

Keywords: age-related eye diseases, exudative age-related macular degeneration, visual evoked potential, optical coherence tomography, visual acuity

Introduction

The age-related macular degeneration (AMD) diagnosis is mainly based on biomicroscopy examination, optical coherence tomography (OCT) and/or fluorescein angiography (FAG). AMD is classified to dry atrophic and wet exudative forms. In wet AMD, choroidal neovascularization arises as capillary-like structures with multiple points of origin and causes serous detachment of the RPE or retina, haemorrhages, lipid exudation and thickening of the retina (Kaarziranta et al. 2011; 2013; Kinunen et al. 2012). Vision loss occurs through the structural and metabolic damage in retina and RPE cells. The activity in neovascular membranes has been successfully suppressed by different anti-VEGF agent (bevacizumab, ranibizumab and aflibercept) intravitreal injections. These compounds have comparable safety profiles and treatment efficacy (Catt Research Group et al. 2011; Heier et al. 2012; Chakravarthy et al. 2013).

Presently OCT is a standard technique for anatomical imaging of the retina. It provides noninvasive, objective and reproducible quantitative measurements of macular thickness and volume (Hunter et al. 2013). It provides a useful tool for diagnosis and monitoring the response to anti-VEGF intravitreal injection. In the literature, there is no clear consensus regarding the anatomic points at which the retinal thickness should be measured. At the other end of the visual processing stream, visual evoked potentials (VEP) provide quantitative information on the functional integrity of the visual pathways in the central nervous system. VEPs are considered to be more sensitive in detection of optic neuritis and clinically silent lesions in multiple sclerosis than MR imaging (Ko 2010).

The effects of macular diseases on VEP are well established (Marcus et al. 1983; Folk et al. 1984; Bass et al. 1985; Sherman et al. 1986; Johnson et al. 1987; Shimada et al. 1997; Sabeti et al. 2013), but there are only a few previous studies where patients are treated for wet AMD and the possible modulation of their VEP are followed (Macky & Mahgoub 2012). In our previous study, we have shown that beneficial anti-VEGF injections of wet-AMD patients improve the VEP markers (Vottonen et al. 2013). Links between the changes in visual acuity, OCT and VEP parameters are poorly understood.

The number of wet AMD patients is a heavy burden to ophthalmology clinics in the Western countries. The treatment strategies and patient follow-up are mainly based on BCVA and OCT findings. We wanted to investigate whether VEP could offer a novel instrument for diagnosis and/or monitoring of the patients in order to improve the selection of the cases most likely benefiting from anti-VEGF treatment. Also, we tested between two anatomical locations for measuring retinal thickness from OCT and investigated whether retinal volume would be a more accurate parameter than retinal thickness for monitoring AMD patients.

The aim of the present study was to investigate the influence of the decreased intraretinal fluid in the function of visual pathways and visual acuity. Our hypothesis was that an association could be detected between the changes in VEPs and the improvement of vision and decreased retinal fluid for wet AMD patients. Moreover, we wanted to assess the feasibility of VEP as a novel monitoring tool for these patients.

Materials and methods

We performed a prospective non-randomized interventional study. All the patients enrolled in the study were above 65 years of age. Exclusion criteria were: history of previous intravitreal treatment, diabetes, glaucoma in the study eye, history of previous intraocular surgery (cataract surgery without complications was accepted) or laser treatment of the eyes. The duration of the active disease was estimated according to the patient’s history from the beginning of visual symptoms including decreased visual acuity, blurring of vision or metamorphopsia. The patient should not have had these symptoms for more than 3 months in order to enter this study. Ethics Committee of the Kuopio University Hospital had approved the study and the tenets of the Declaration of Helsinki were followed. All participants signed an informed consent.

The interventional study group consisted of 16 patients having exudative AMD and the control group consisted of six pseudophakic patients. One treated eye was excluded due to a RPE tear and three fellow eyes were excluded due to development of wet AMD during the study. Diagnosis was based on the best corrected visual acuity (BCVA) testing (converted to logMAR for statistical analysis), full biomicroscopy examination and OCT (Spectral OCT/SLO, Ophthalmic Technologies Inc., Toronto, Canada or Spectralis Heidelberg Engineering, Heidelberg, Germany) analysis in the Department of Ophthalmology, Kuopio University Hospital. The patient demographics and BCVA data are shown in Table 3. For the patients at their first visit, when exudative AMD diagnosis was made, anti-VEGF (bevacizumab) intravitreal injection was applied to the affected eye. Intravitreal injections were applied three times, separated by 4–6 weeks. Visual evoked potentials (VEP), BCVA testing, full biomicroscopy examination and OCT analysis were performed at the first visit prior to anti-VEGF injection and after 4–6 weeks of the last (i.e. third) injection. Thus, there were 16–18 weeks between all the baseline and follow-up measurements. For the control group the follow-up examination was performed about 14 weeks after the first study visit.

Optical coherence tomography

Automated retinal thickness values provided by the OCT equipment was used when appropriate and when detection was reliable. If detection errors in the automated system were noted, the corrections were performed manually by a single researcher (PV).
Two different thickness measurements were made from the centre of the fovea. If the placement of fovea was not obvious due to oedema, anatomical comparison to the OCT of other eye was made and the place of fovea was determined on the basis of symmetry. The first measurement was made from the inner limiting membrane (ILM) to the top of the retinal pigment epithelium (RPE) and the second from ILM to the top of Bruch membrane (BM). The volumes were automated measurements from ILM to BM provided by Heidelberg Spectralis OCT.

**Visual evoked potential**

Visual evoked potentials were recorded using a 64-channel electrode cap (EasyCap, Falk-Minow Services, Germany). Data were collected with the SynAmps2 amplifier (Neuroscan, Texas, USA). The midline centrofrontal electrode (FCz) served as reference for all scalp electrodes. Electrodes were placed on the skin above and below the right eye for a bipolar recording of vertical electro-oculogram activity (VEOG). Contact impedance of all scalp electrodes was kept below 10 kΩ. The sampling rate was set to 500 Hz per channel with a recording bandpass of 0.1–50 Hz.

A high-contrast black and white reversing checkerboard stimulus with a check size of 35 min of arc was presented on a computer monitor using STIM2 software (Neuroscan, Texas, USA). A circular stimulus subtending to a diameter of 10.3 degrees of visual angle was used in order to cover the macular area. The pattern was reversed at a rate of one reversal per second. A red dot placed at two check widths above the center of the stimulus was used as a fixation mark. Viewing distance was 100 cm. Stimulation was monocular with the other eye occluded. Responses to two consecutive blocks of 120 stimuli were recorded with an undilated pupil for each eye and recording session. There was a short resting break between the blocks. Full refractive correction was used. The non-affected eye was recorded first in both the pre- and post-treatment sessions. Each patient could see the fixation mark with the non-affected eye. If the patient could not see the fixation mark with the eye affected by wet AMD, he/she was asked to fixate at its known location.

The VEP data were analyzed offline with scan software (Neuroscan, Texas, USA). The continuous data from two recording blocks were merged into one file. After high-pass filtering at 1 Hz, the data were transformed to epochs of 350 milliseconds duration, including a 50-millisecond prestimulus baseline interval. The data were checked both automatically and visually and epochs containing blinks or other artefacts were manually rejected. The artefact-free epochs were then averaged separately for each eye and each recording session. The baseline-to-peak amplitude and the latency of P100 peak at electrode Oz were measured for further analysis.

To check that the P100 parameters in the response could be reliably measured, we used point-wise t statistics as a measure of signal-to-noise ratio. This statistic takes into account the amplitude, standard deviation and number of sweeps in the average. If the t value was smaller than 1.97 (corresponding to a p value of 0.05 when there were ~200 sweeps in the average) over the range of 80–170 milliseconds, the amplitude was not significantly different from zero at any of the time points. This was the case in the treated eye of two patients. In these cases, the P100 amplitude was set to zero and the latency value left blank since it could not be reliably measured.

**Statistical analysis**

The statistical analysis was done using spss® Statistics for Windows, Version 19.0 (SPSS inc., Chicago, IL, USA). The level of statistical significance was set at p < 0.05. Wilcoxon’s signed-rank test was used to determine if differences between the baseline and follow-up measurement values were statistically significant. Linear relationships between the relative changes of variables from the baseline to follow-up were tested using Pearson’s correlation coefficient.

**Results**

A total of 22 patients entered the study; there were 16 treated patients and six control patients. There were no significant changes of visual acuity, OCT or VEP markers in the control group (see Table 4) emphasizing the reliability of the study method. As for the intervention group, in the treated eyes, the mean logMAR BCVA improved significantly (p < 0.05), from 0.69 ± 0.32 units at baseline to 0.51 ± 0.37 units at follow-up. The baseline and follow-up measures of visual acuity (logMAR), retinal thicknesses, and VEP amplitude and VEP latency are shown in Table 4. The retinal volume change was measured from six AMD patients and from the control group. In the treated group, both of the retinal thickness measurements improved significantly: from ILM to the top of the RPE and from ILM to the BM. In VEPs, significant changes occurred in P100 amplitudes, but not in the latencies. The changes in VEP are illustrated in Fig. 12. A box plot of VEP amplitude before and after the anti-VEGF treatment are shown in Fig. 13. In the fellow eyes, there were no significant changes in the measured parameters.

The relative changes from baseline to follow-up of VEP amplitude and retinal thickness from ILM to BM correlated significantly r = −0.630 (p < 0.05) as well as retinal thickness from ILM to RPE r = −0.668 (p < 0.05). Also BCVA (logMAR) and retinal thickness from ILM to BM correlated significantly r = 0.576 (p < 0.05). The relative changes of retinal volume correlated significantly with BCVA (logMAR) r = 0.989 (p < 0.01), with VEP amplitude r = −0.819 (p < 0.05) and with
Table 4. Comparison of baseline and follow-up characteristics and the amount of change.

<table>
<thead>
<tr>
<th>AMD patients’ treated eyes mean (±SD)</th>
<th>N</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity, logMAR</td>
<td>15</td>
<td>0.69(±0.32)</td>
<td>0.51(±0.37)</td>
<td>-0.18(±0.32)</td>
<td>0.038</td>
</tr>
<tr>
<td>Retinal thickness, µm (ILM-RPE)</td>
<td>15</td>
<td>330(±130)</td>
<td>190(±130)</td>
<td>-100(±140)</td>
<td>0.023</td>
</tr>
<tr>
<td>Retinal thickness, µm (ILM-BM)</td>
<td>15</td>
<td>490(±170)</td>
<td>320(±220)</td>
<td>-170(±200)</td>
<td>0.009</td>
</tr>
<tr>
<td>Retinal volume, µm³</td>
<td>5</td>
<td>0.3(±0.1)</td>
<td>0.3(±0.2)</td>
<td>-0.1(±0.1)</td>
<td>0.046</td>
</tr>
<tr>
<td>VEP amplitude P100</td>
<td>15</td>
<td>4.2(±4.0)</td>
<td>5.2(±4.7)</td>
<td>1.0(±1.4)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

AMD patients’ fellow eyes mean (±SD)

| Visual acuity, logMAR                | 13| 0.26(±0.24) | 0.26(±0.25) | 0.00(±0.19) | 0.799 |
| Retinal thickness, µm (ILM-RPE)      | 13| 190(±60)    | 200(±70)    | 10(±50)    | 0.575 |
| Retinal thickness, µm (ILM-BM)       | 13| 230(±60)    | 240(±60)    | 10(±20)    | 0.441 |
| Retinal volume, µm³                  | 5 | 0.2(±0.1)   | 0.2(±0.1)   | 0.0(±0.0)  | 0.157 |
| VEP amplitude P100                   | 13| 6.9(±4.4)   | 6.7(±4.0)   | -0.18(±1.5) | 0.346 |

Control patients’ eyes mean (±SD)

| Visual acuity, logMAR                | 12| 0.04(±0.06) | 0.06(±0.08) | 0.01(±0.03) | 0.109 |
| Retinal thickness, µm (ILM-RPE)      | 12| 200(±10)    | 200(±20)    | 10(±10)    | 0.688 |
| Retinal thickness, µm (ILM-BM)       | 12| 220(±10)    | 220(±10)    | 10(±10)    | 0.472 |
| Retinal volume, µm³                  | 12| 0.2(±0.0)   | 0.2(±0.0)   | 0.0(±0.0)  | 0.157 |
| VEP amplitude P100                   | 12| 10.6(±2.7)  | 11.1(±2.7)  | 0.4(±1.5)  | 0.347 |

BM = Bruch membrane, ILM = inner limiting membrane, RPE = retinal pigment epithelium.

* Mann–Whitney U test.

Discussion

In this study, we provide evidence that the increase in VEP amplitude and the improvement in BCVA are correlated with the decrease in retinal thickness in treated wet AMD patients.

Recently, we reported a decrease in P100 latency in the treated eye (Vottoen et al. 2013). In this work with a larger sample size we found no change in latency. Even though the grand average waveforms (Fig. 12) support this conclusion, the finding can be questioned. We could not define the P100 latency in the VEPs of two treated eyes since the VEP waveform was not significantly different from zero at any time point in the range of 80–180 mseconds. We set the upper limit of the range to 180 mseconds because one could argue that there might be a P100 response present at latencies even longer than 150 mseconds. There are no studies examining how much the blurry or blind spots in the visual field of wet AMD patients would affect the VEP latencies. However, in the study of Yadav et al. (2012) – that in practice simulates the situation – shows that that a circular blank field of 15 degrees in the centre of 17 × 15 degrees checkerboard field increases the P100 latency maximally from about 110–40 mseconds. Thus it is very likely that the missing P100 responses are not extremely delayed but just too small to be discerned from the noise.

Omitting the missing data is by far the most common approach in the literature in cases like this. For this to be a valid procedure, one should be certain that the data are missing completely at random. Since the other of our patients with missing data had the poorest visual acuity of our patient material, the requirement of missing at random may not be fulfilled. With correlations, the danger of biased results due to omission of missing data is even bigger and we cannot draw any statistical inferences on the latency data.

One should note that even though there were two treated eyes in our material in which the P100 peak could not be identified, the overall reliability of the VEP responses even in the affected eye before the treatment was good. The median t value at the P100 peak was 5.09, which corresponds to p < 0.000001.

During the last years, technological development of OCT has been relatively fast. Resolution of the recording has improved, but retinal thickness measurements are based on the standardization of OCT equipment that may vary between models. Based on the present study, there does not appear to be clinically superior method of measuring retinal thickness by OCT. The measurements from ILM to the top of RPE and from ILM to the top of BM are both highly correlated with BCVA and VEP amplitude. In addition, retinal volume is highly correlated with BCVA and retinal thickness. We can conclude that in monitoring the wet AMD patients either with BCVA or OCT is equally valuable and either could solely be used for the treatment decision. Since OCT is a rapid examination method, it could

Fig. 12. On the left, grand average waveforms of visual evoked potentials in the Oz-FCz derivation before (thin line) and after (thick line) anti-VEFG treatment from the treated eye of 15 patients. On the right, the grand average waveforms from both eyes of six controls with a similar time interval but no treatment between the recordings. Note the different scaling between the patient and control waveforms – the P100 amplitude of the controls is more than twice that of the in the AMD patients even after the treatment.

Fig. 13. Box plot of visual evoked potential amplitude before (baseline) and after anti-VEFG treatment in the treated eye of 15 patients. Box and whiskers depict the minimum and maximum values (lower and upper whiskers respectively), the first and third quartile (lower and upper limits of the box, respectively) and the median (solid line through the box). The small black square depicts the mean value.
be prioritized for the decision to start the treatment and for the follow-up. According to a multicentre cohort study (SEVEN UP), monthly OCT follow-up is recommended (Rofagha et al. 2013). The present study does not indicate additional usefulness of VEP in the diagnosis or monitoring of wet AMD patients. VEP, as performed here, does not seem to offer an instrument for designing more individualized treatment protocols. However, VEP recordings provided unequivocal evidence of recovery in the crucial upstream visual processing initiated by intravitreal anti-VEGF treatment in the affected eyes. Checkerboard VEP responses in the visual cortex originate mainly from stimulation of the macula and central visual field and depend on functional integrity of central vision at any level of the visual pathway (Odom et al. 2016). The untreated phase of AMD can be considered also as a sensory deprivation state in the visual cortex and the recovery in the affected eye VEP amplitude after successful treatment implies that the visual cortex can recover from that deprivation state. However, the after-treatment VEP amplitude of the affected eye remains somewhat smaller than that of the fellow eye, as does also the acuity, indicating that the recovery is not complete. The reason might be retinal, i.e., that the retinal input has not been fully recovered. Some evidence against this is that the retinal thickness values show nearly completely recovery. Another explanation is that there are plastic changes in the cortex during the deprivation state and when the input returns to normal or nearly normal, other plastic changes are needed to bring back the normal vision. In our elderly subjects, some of the changes that have happened during the deprivation may be difficult to reverse. The cortical mechanisms responsible for amplitude recovery may correspond, at least in part, to those mechanisms extensively studied in use-dependent neural plasticity. In that area, human and experimental animal research has confirmed that sensory and motor cortices undergo extensive reorganization.

**Abstract**

**Background:** The early symptoms of wet age-related macular degeneration (AMD) include a difficulty in face recognition. Our aim was to evaluate the visual processing of faces in AMD patients and whether this would be improved by anti-VEGF therapy.

**Design:** This was a prospective interventional cohort study.

**Participants:** Twelve patients with monocular wet AMD and six control subjects were recruited.

**Methods:** Patients received three bevacizumab intravitreal injections into the single affected eye. Face detection processes were studied in the brain using cortical event-related potentials. Face pictures were shown as targets (16.7%) among standard pictures of pixelated faces in an oddball-type paradigm.

**Main outcome measures:** The main outcome measures were visual acuity, electrophysiological recordings of the face task and optical coherence parameters, which were all measured at the baseline and 4–6 weeks after the last injection. The results were compared between the baseline and follow-up measurements.

**Results:** Face pictures elicited well-defined electrical components in occipital and parieto-occipital cortical areas at baseline and after treatment. The face-specific N170 component was evident in all subjects with longer peak latency in patients than in controls (170 ± 13 versus 155 ± 14, p = 0.032). Unexpectedly an early unintentional prediction of perceiving a face, i.e. deviance-related negativity, was present in patients and controls. Visual acuity of the affected eye seemed to improve in patients from logMAR 0.71 (±0.33) to 0.52 (±0.39) by 119 (±23) days without any accompanying significant change in face-specific electrical potentials.

**Conclusions:** Monocular wet AMD distinctly influenced face-specific brain electrophysiological components. However, the anti-VEGF treatment did not improve the binocular face detection ability.

**Keywords:** age-related eye diseases, bevacizumab, face detection, EEG, N170

**Introduction**

Wet age-related macular degeneration (AMD) is a well-known risk factor for blindness in the elderly and a major concern in ophthalmology clinics. Long before the AMD patient reaches the stage of legal blindness, one of the first reported symptoms is a difficulty in face recognition in daily life (Bullimore et al. 1991). Since face detection and recognition are such an important aspect of social interaction, it is evident that AMD may have a major social cost as well as exerting an economical...
impact on an individual’s life. Moreover, it is also a risk factor for hip fractures and depression as well as reducing the quality of life (Brody et al. 2001; Rovner et al. 2002; Ivers et al. 2003). The recently developed anti-VEGF drugs represent the first therapies that prevent moderate and severe vision loss in nearly all neovascular AMD patients and these agents are able to improve visual acuity (VA) in the majority of patients. Visual acuity or decreased contrast sensitivity may severely affect the face recognition ability in older adults. Face identification and performance in a behavioral face matching task have been shown to be slower in patients with binocular AMD (Barnes et al. 2011).

The face recognition capability starts to develop during the first months after birth with early visual input to the right hemisphere being especially important. A deprivation of patterned visual stimuli during the first months of life, for example due to congenital cataract, causes permanent deficits in the expert face processing (de Grand et al. 2001, 2003; Mondloch et al. 2013). Face recognition is a complex task involving mainly three regions of brain: inferior occipital gyrus, superior temporal sulcus and lateral fusiform gyrus. It has been debated whether face is a specific stimulus to the brain, for example, lesion studies have revealed an inability to recognize facial identity and expression although other objects are still correctly identified (Kanwisher et al. 1997; Calder & Young 2005; Dekowska et al. 2008; Barnes et al. 2011). Brain imaging with electrophysiologic (EEG, ERP, MEG) and metabolic examinations (PET, fMRI) offer tools to investigate the mechanisms involved in face recognition (Labar et al. 2003; Fairhall & Ishai 2007; Dekowska et al. 2008), but very little is known about visual processing of faces in AMD patients.

Usually AMD does not affect both eyes evenly; thus the two monocular visual acuities generally differ considerably. Patients with AMD have reduced binocular contrast summation and binocular inhibition i.e. binocular performance is worse than that of the better eye alone (Valberg & Fosse 2002; Tarita-Nistor et al. 2006). AMD also impairs the fixation stability (Bellmann et al. 2004). After the treatment of wet AMD with ranibizumab injections, there appears to be an improvement in the fixation stability (Gonzalez et al. 2011).

Repeated intravitreal anti-VEGF injections are the current treatment of wet AMD and these administrations improve patient-reported vision-related function (Chakravarthy et al. 2013). Consequently, it is also important to understand the possible changes in complex visual processes such as face recognition in AMD patients. Since also visual acuity may affect the face recognition ability, our patients were subjected to a face task with an odd-ball-type design and their performance was evaluated by measuring event-related potentials. All of our patients had one wet AMD eye. We followed them through the treatment with intravitreal anti-VEGF injections to investigate if the treatment changed the electrophysiological markers of face recognition. Our control group also performed the same tasks at the same time intervals.

**Methods**

**Study setting and population**

This prospective nonrandomized interventional study was performed with AMD patients and healthy controls. The patients’ mean age was 80 ± 7 years. There were the following exclusion criteria: history of previous intravitreal treatment, diabetes, glaucoma in the study eye, history of previous intraocular surgery (cataract surgery without complications was accepted) or laser treatment of the eyes. The duration of the active AMD disease was estimated according to the patient’s history from the beginning of visual symptoms including decreased visual acuity, blurring of vision or metamorphopsia. The patient should not have had these symptoms for more than three months in order to enter this study. The control group (mean age 72 ± 6 years) had no history of eye or neurological diseases. The Ethics Committee of the Kuopio University Hospital approved the study and the tenets of the Declaration of Helsinki were followed. All participants signed an informed consent.

**Clinical examination and treatment**

The intervention group consisted of 12 patients with exudative AMD and the control group consisted of six pseudophakic patients. Diagnosis was based on the best corrected visual acuity (BCVA) testing (converted to logMAR in the statistical analysis), full biomicroscopy examination and OCT (Spectral OCT/SLO, Ophthalmic Technologies Inc., Toronto, Canada or Spectralis Heidelberg Engineering, Heidelberg, Germany) analysis in the Department of Ophthalmology, Kuopio University Hospital. The patient demographics and BCVA data are shown in Table 1. For the patients on their first visit, when the diagnosis of exudative AMD was made, an anti-VEGF (bevacizumab) intravitreal injection was administered into the affected eye. Intravitreal injections were delivered three times separated by 4–6 weeks. Event-related potentials with whole-head EEG, BCVA testing, full biomicroscopy examination and OCT analysis were performed at the first visit prior to the first anti-VEGF injection and after 4–6 weeks after the last (i.e. third) injection. There were 16–18 weeks between the baseline and follow-up measurements for patients and controls.

**Stimulation and recording**

Event related potentials (ERP) were recorded using a 64-channel electrode cap (EasyCap, Falk-Minow Services, Germany). Data were collected with the SynAmp2 amplifier (Neuroscan, Texas, USA). The midline centrofrontal electrode (FCz) served as the reference for all scalp electrodes. Additional electrodes were placed on the skin above and below the right eye for a bipolar recording of vertical electro-oculogram activity (VEOG). Contact impedance of all scalp electrodes was kept below 10 kΩ. The sampling rate was set to 500 Hz per channel with a recording bandpass of 0.1–50 Hz.

Ten grayscale face images (five male, five female) were selected from the Pictures of Facial Affect of Ekman and Friesen (1976). The faces were all with a neutral expression and in a frontal view. For each image, a pixelated version was made with the reference for all scalpel electrodes. Additional electrodes were placed on the skin above and below the right eye for a bipolar recording of vertical electro-oculogram activity (VEOG). Contact impedance of all scalp electrodes was kept below 10 kΩ. The sampling rate was set to 500 Hz per channel with a recording bandpass of 0.1–50 Hz.
mask could be used for all images. From a viewing distance of 100 cm, the major axis of the elliptical image was 10 degrees and the minor axis 6.6 degrees of visual angle.

The images were presented on a computer monitor using STIM2 software (Neuroscan, Texas, USA). The pixelated images served as standard stimuli and the real-face images as targets in an active oddball task. The subject had to press a button when seeing a real-face image. Response accuracy and reaction times of the button presses were recorded with the EEG data.

The duration of each standard and target stimulus was 306.7 ms and the intersimulus interval was 1506 ms. One recording session consisted of two blocks, each having 300 stimuli. There was a brief resting pause between the blocks. Each target image was presented five times and each pixelated image was shown 25 times in a block in a randomized order. Thus, the proportion of targets was 16.7%. Stimulation was binocular and the interstimulus interval was 1000 ms.

Data analysis

The ERP data were analyzed offline with SCAN software (Neuroscan, Texas, USA). The continuous data from two recording blocks were merged into one file. Then the data were filtered digitally with a zero-phase shift bandpass filter to 1–30 Hz (3 dB points of 24 dB/octave roll-off). To avoid data loss by a blink artifact, the eye movement reduction technique described by Semlitsch et al. (1986) was applied to the filtered data. The data were then transformed to epochs of 1000 ms duration, including a 100 ms prestimulus baseline interval. For each channel and epoch, the mean amplitude of the baseline was subtracted from all time points. Epochs with artifacts exceeding ±30 μV at any of the frontal electrodes were automatically rejected. In addition, the data were checked visually and epochs containing suspected artifacts in any channel were rejected. The FCz-referenced epochs were then re-referenced to the common average and averaged separately for standard and target trials.

The latency and baseline-to-peak amplitude of the face-specific N170 component was measured from the time of the target stimulus to correct responses (real face pictures) were obtained. The number of errors was also analyzed. An error was counted if there was no response to the target, or the response occurred more than 1000 ms after the target stimulus onset, or when a response was made to a standard stimulus.

Statistical analysis

Means and standard deviations of the amplitudes and latencies of major electrophysiological components as well as of the behavioral data (reaction times, number of errors and misses) were calculated. The statistical analysis was done with spss® Statistics for Windows, Version 19.0 (SPSS Inc., Chicago, IL, USA). The level of statistical significance was set at p < 0.05. Wilcoxon signed-rank test was used to determine if differences between the baseline and follow-up measurement values were statistically significant. Mann-Whitney U-test was used to compare the patients and the control subjects.

Results

Twelve patients were treated with three anti-VEGF injections and six control subjects were monitored for a corresponding period (for subject characteristics, see Table 5). A significant treatment effect was seen in the retinal thickness (p = 0.004) and a trend toward a significant effect in the visual acuity (p = 0.091) was present in the AMD patients. No significant changes in visual acuity, OCT or electrophysiological markers of face recognition were observed in the control group during the follow-up (see Table 6).

Electrophysiologic analysis of the face recognition task revealed high amplitude N170 components in both patients and controls. N170 occurred significantly earlier (p = 0.032) in the control group than in patients before the treatment. This difference was not detected any longer after the follow-up (Table 7). Occipital and posterior-temporal recordings of face (target) and pixelated face (standard) stimuli in patients are shown in Fig. 14. Neither patients nor controls exhibited any significant differences in the ERP component characteristics (latencies, amplitudes) elicited by face stimulus between baseline and follow-up recordings. As our task design allowed for the formation of difference waveforms (target minus standard) to analyse specifically and exclusively face recognition, those difference waveforms were calculated. The face-specific N170 was followed by deviance-related negativity (DRN, see in Fig. 14), which peaked around 250 ms. DRN is clearly seen in Fig. 15, where the shaded area denotes the time window for the mean amplitude calculation for DRN. The mean amplitudes of DRN did not differ significantly between patients and controls, nor did DRN change between baseline and follow-up (Table 7). Nonetheless, a tendency towards a higher amplitude is seen in patients especially in the before-treatment recording (Fig. 15, electrode PO8). These two components, N170 and DRN, elicited by the rarely presented face pictures most likely originate from different sources.

Table 5. Characteristics of patients and control subjects. Note, that both the right and the left eye served as a control eye of the control subjects.

<table>
<thead>
<tr>
<th></th>
<th>AMD patients</th>
<th>Controls</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year ± SD)</td>
<td>79.6(±7.0)</td>
<td>72.3(±5.8)</td>
<td>0.053</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>4/8</td>
<td>2/4</td>
<td>–</td>
</tr>
<tr>
<td>Treated eye (Right/Left)</td>
<td>4/8</td>
<td>6/6</td>
<td>–</td>
</tr>
<tr>
<td>Follow-up time (days)</td>
<td>119(±23)</td>
<td>96(±4)</td>
<td>0.151</td>
</tr>
<tr>
<td>Smoking (Yes/Occasionally/No)</td>
<td>0/3/9</td>
<td>0/1/5</td>
<td>–</td>
</tr>
<tr>
<td>BMI (±SD)</td>
<td>26.3(±4.9)</td>
<td>27.0(±3.7)</td>
<td>0.616</td>
</tr>
</tbody>
</table>

BMI = body mass index.

* p Values were calculated using the Mann-Whitney U test.
**Table 6.** Vision and OCT data at baseline (mean±SD) and follow-up and the amount of change.

<table>
<thead>
<tr>
<th>AMD patients: treated eyes</th>
<th>N</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity, logMAR</td>
<td>12</td>
<td>0.71±0.33</td>
<td>0.52±0.39</td>
<td>−0.19±0.36</td>
<td>0.091</td>
</tr>
<tr>
<td>Retinal thickness, μm (ILM-RPE)</td>
<td>12</td>
<td>320±130</td>
<td>200±150</td>
<td>−120±100</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**AMD patients: fellow eyes**

| Visual acuity, logMAR     | 12    | 0.20±0.16         | 0.20±0.20         | 0.00±0.17       | 0.528|
| Retinal thickness, μm (ILM-RPE) | 12 | 220±60            | 200±50            | −20±60          | 0.610|

**Control subjects**

| Visual acuity, logMAR     | 6     | 0.04±0.06         | 0.06±0.08         | 0.01±0.03       | 0.109|
| Retinal thickness, μm (ILM-RPE) | 6 | 200±10            | 200±20            | 0±10            | 0.688|

ILM = inner limiting membrane; RPE = retinal pigment epithelium.

* p values were calculated using the Wilcoxon Signed Rank test.

**Table 7.** The comparison of ERP characteristics at Oz between patients and controls at the baseline and follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Baseline controls</th>
<th>Baseline patients</th>
<th>Follow-up controls</th>
<th>Follow-up patients</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N170 latency (mseconds)</td>
<td>155±14</td>
<td>170±13</td>
<td>0.032</td>
<td>154±18</td>
<td>172±13</td>
</tr>
<tr>
<td>N170 amplitude (μV)</td>
<td>−4.6±2.8</td>
<td>−6.5±4.1</td>
<td>0.335</td>
<td>−6.7±3.5</td>
<td>−6.5±5.0</td>
</tr>
<tr>
<td>DRN amplitude (μV)</td>
<td>−2.2±2.2</td>
<td>−3.8±2.8</td>
<td>0.335</td>
<td>−2.6±6</td>
<td>−3.5±2.7</td>
</tr>
<tr>
<td>Reaction time (mseconds)</td>
<td>384±44</td>
<td>437±73</td>
<td>0.151</td>
<td>396±71</td>
<td>436±67</td>
</tr>
<tr>
<td>Errors (n)</td>
<td>1.7±1.9</td>
<td>3.8±3.8</td>
<td>0.250</td>
<td>0.8±0.7</td>
<td>3.3±3.1</td>
</tr>
<tr>
<td>Misses (n)</td>
<td>0.2±0.4</td>
<td>2.0±3.4</td>
<td>0.180</td>
<td>0.2±0.4</td>
<td>1.73±3.0</td>
</tr>
</tbody>
</table>

*p values were calculated with the Mann–Whitney U test.

**Fig. 14.** Grand average waveforms for standard (thin line, pixelated face) and target (thick line, real face) stimuli in two electrode locations, Oz and PO8, before and after treatment in 12 AMD patients. Oz is located on the top of the primary visual area and the face-selective 170 mseconds component is larger for real-face stimuli (target) than for pixelated face stimuli (standard) and shows a double amplitude for the target stimulus (note μV scale).

The DRN component was observed as a negative deflection followed by a positive deflection, called P300. The well-known ERP component, P300, is widely agreed to indicate conscious context updating. Hence DRN occurred well before the conscious recognition process of the real face.

Behavioural data of the reaction times to seeing a real face were registered and those tended to be slightly longer (non-significantly) in patients than in controls. Furthermore, making errors (being late or pushing a button for a standard stimulus) also tended to be more common among patients than in controls, albeit not statistically significantly (see Table 7).

**Discussion**

The effects of AMD and its current treatment in any specific cortical visual processes have been only occasionally studied. Individual patient investigations using functional MRI analysis have examined the reorganization in the visual cortex caused by AMD (Dilks et al. 2009, 2014). However, the positive and/or negative effects of these new routine injection treatments have been largely overlooked. There are only two groups that have assessed visual evoked potentials (VEP) of wet AMD patients after anti-VEGF injections (Macky & Mahgoub 2012; Vottonen et al. 2013, 2015). The electrophysiological parameters of face recognition in this context have not been reported earlier.

The neurophysiological methods used in this study are widely considered to be reliable real-time markers of the cognitive processes elicited by a given task. The present visual task was a rather conventional oddball paradigm, where subjects were requested to press a button when seeing a real face among the standard elliptical grayscale stimuli. Behaviourally task performance was not markedly impaired in AMD patients compared to controls even though a tendency toward slower responses was detected. The ERP component N170 latency was shorter in healthy controls than in patients however, the waveform configurations and amplitudes obtained here were similar to those in the literature (Mnatsakanian & Tarkka 2004; Bentin et al. 2006; Bindemann et al. 2008). Furthermore, the injection therapy did not significantly alter the analyzed ERP parameters. The fact that these
parameters remained relatively unaltered, even though there was a clear treatment effect in the retinal thickness and visual acuity in the treated eye, is probably best explained by the binocular nature of the present test. In the present data, we cannot separate the roles of individual eyes but it is likely that there was only a minor effect from the worse eye during the test.

Our standard stimuli, an ellipsoid without facial characteristics, elicited a VEP component with a peak latency at about 160–170 mseconds. The real face stimuli elicited the N170 component, which manifests early detection of faces, and this stimulus almost doubled its amplitude in the scalp area above the fusiform gyrus (see Fig. 14). This rather typical high-amplitude N170 was somewhat unexpectedly followed by a prominent deviance-related negativity (DRN) component. DRN is a recognized component in visual mismatch negativity studies reflecting aspects of task difficulty (Kimura & Takeda 2013). Here the DRN can be seen as a negative deflection at about 250 mseconds in the parieto-occipital recording location. However, it is temporally more separated in the occipital recording site (see Figs 14 and 15). The difference waveform analysis of target waveforms further clarified the temporal separation and distinctly detached processes of the N170 and DRN.

The N170 component elicited by a face picture activates occipito-temporal brain areas, mainly the fusiform gyri, as displayed also in the N170 scalp distribution (Fig. 16). The current component configuration and scalp distribution are in good agreement with previous neutral face stimulus analyses (Mnatsakanian & Tarkka 2004; Bentin et al. 2006; Bindemann et al. 2008). The scalp distributions of DRN and N170 appear to be different (see Fig. 16). This difference further supports our view that N170 and DRN are separate processes both elicited by the same face picture. According to psychophysiological models of human face processing, faces are first detected from their environment during a structural encoding stage, which is followed by the recognition phase during which the individual face will be identified (Haxby et al. 2000). The 250 mseconds component, which here is called DRN, has also been thought to reflect a face stimulus repetition effect (Begleiter et al. 1995; Schweinberger et al. 2004; Neumann & Schweinberger 2008). Binding et al. (2008) demonstrated that N250r was strongest to unprimed faces compared to primed face pictures. Our task corresponds to unprimed face stimuli as no naming or matching was required from our subjects. Hanso et al. (2010) used pixelated images to study the effects of spatial quantification on ERP signatures of familiar versus unfamiliar face perception. They found a stronger negative component for fine and intermediate scale pixelation, but not for coarsely quantized facial images. In spatial frequency terms, their finely and coarsely quantized images are close to our real-face and pixelated images, respectively, and thus the component they called N250r is very likely the same as we have termed DRN. Fortunately, there is one way to determine whether repetition or deviance makes the greatest contribution to this component. Our participants had not seen the images before and thus there could be no repetition effect in their response to the first occurrence of an individual real face image in the baseline recording. We calculated the grand average of these responses and found that it did not differ from the grand average of the responses over all real face images, apart from being somewhat noisier due to the much smaller number of sweeps.
on the average. Thus, the component at around 250 mseconds exists already before stimulus repetition and must be related to either some general or a face-specific deviance detection. It is possible that the DRN reflects the deviant stimulus triggered by accessing the memory storage of previous faces against which a perceived face image is compared. DRN may be a marker of the comparison process already before the conscious recognition process. This component may well be one of the tools to account for the speed and efficiency at which humans are able to identify faces. The AMD patients' waveform in Fig. 15 suggests that the DRN amplitude could be larger in patients than in controls. The present finding is not statistically significant but does suggest that the larger amplitude in the AMD patients may reflect their greater difficulty in making a comparison of target face pictures i.e. they need to activate larger neural assemblies.

The anti-VEGF treatment did not alter the face detection parameters in AMD patients. Even though, no deterioration occurred in any of the measured amplitudes after the 14–16 weeks’ period as expected. This supports the positive effect of anti-VEGF treatment, also evident in the OCT results. The binocular nature of this test simulates patients’ everyday tasks and take into account the low importance of the vision of the worse eye. The quality of life and the ability to perform normal activities of daily living (ADL) are highly influenced by the vision of the better seeing eye only (Brown 1999; McClure et al. 2000). This may further imply that the effect of only one affected eye on quality of life is rather low.

We recognize that by using binocular task performance in this patient group, we have somewhat limited the utilization of our results in psychophysical face recognition research. Future studies should assess binocular visual acuity and conduct experiments separately for each eye. There is a slight age difference between our patients and controls, but this most likely exerted no influence on the present results. In further studies, larger and more homogenous groups should be evaluated.

Acknowledgements
The authors want to thank the participants and Helvi Kämänäinen (Kuopio University Hospital), RN, for technical assistance. The authors declare no financial disclosures.

Cost-Effectiveness of Treating Wet Age-Related Macular Degeneration at the Kuopio University Hospital in Finland Based on a Two-Eye Markov Transition Model

Abstract

Purpose: Wet age-related macular degeneration (AMD) is the leading cause of blindness worldwide, although it can now be treated with regular intraocular anti-VEGF injections. In this study, we wanted to evaluate whether less frequent injections of aflibercept would make it more cost effective when compared to ranibizumab and low priced bevacizumab.

Methods: We used a two-eye model to simulate the progression and the treatment of the disease. We selected an eight year period, cycles of three months and five health states based on the visual acuity of the better seeing eye. The transition probabilities and utilities attached to the health states were gathered from previous studies. We conducted the analysis from the hospital perspective and we used the health care costs obtained from Kuopio University Hospital. The costs of intraocular adverse events were taken into account.

Results: The incremental cost effectiveness ratio (ICER) with 3% discount rate (£/QALY) for aflibercept compared to monthly bevacizumab was 1,801,228 and when compared to ranibizumab given as needed, the ICER was minus 3,716,943.

Conclusion: Monthly injected bevacizumab was the most cost effective treatment and monthly ranibizumab the least effective. Since QALYs are largely based on the visual acuity of the better seeing eye, a two eye model should be employed in cost effectiveness studies of any eye which improves visual acuity.

Keywords: exudative age-related macular degeneration, cost-effectiveness, aflibercept, bevacizumab, ranibizumab

Introduction

Neovascular age-related macular degeneration (AMD) is the leading cause of blindness among elderly people in Western countries (Jager et al. 2008). Without treatment, the disease leads to blindness and is responsible for considerable costs (Soubbrane et al. 2007). At the moment there are three different anti-VEGF compounds in use: aflibercept, bevacizumab and ranibizumab (Schmidt et al. 2015). When delivered intravitreally, bevacizumab is used as an off-label medication, and the cost of a single injection is much lower than the other options.

Frequent injections are often needed to keep the disease stabilized (Catt Research Group et al. 2011, Schmidt-Erfurth et al. 2014b). In Finland, the annual number of injections is increasing, leading to an increase in the total costs. When resources are scarce, it is crucial to ensure that treatments are cost effective. The cost effectiveness studies on AMD that have been published to date have some major flaws. Most studies have been based on a one eye model and do not take into account the fact that usually the other eye is not affected and binocular visual acuity (VA) is relatively good (e.g. Raftery et al. 2007; Hernandez-Pastor et al. 2008, 2010; Neubauer et al. 2010; Athanasakis et al. 2012). However, the quality of life years (QALY) depends much more on the visual acuity of the better seeing eye (Brown
et al. 2000). Thus, even though the treatment of the first affected eye already is responsible for high costs, it has only a minor impact on QALYs. A model of chronic eye disease in which the VA of both eyes is impaired, such as is the case of AMD, can only be realistically analysed if both eyes are incorporated into the model. Furthermore, with a chronic progressive disease such as AMD, that needs sustained treatment, the time-horizon should cover the whole treatment period. The current studies are most often limited to time periods of 1–2 years, which does not cover the treatment period of AMD patients (e.g. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group et al. 2012, Dakin et al. 2014). A two-eye model can incorporate the fact that treatment will be started with only one eye. After the other eye becomes affected and also treated, the model can show that there is a much more pronounced impact of treatment on utility.

A Markov transition model can be used to analyse the cost effectiveness of chronic diseases with different health states combined with respectively different utilities and healthcare costs. As a result, the Markov transition model produces an incremental cost effectiveness ratio (ICER), which is defined as the difference in costs between two interventions divided by the difference in their effect (Drummond et al. 2005). In the cost-utility analysis, quality of life years (QALY) is used as the measure of effect.

Our aim was to create a two-eye model, which would take into account the possibility of developing neovascular AMD into the second eye. We developed a Markov transition model to compare the costs and effectiveness of the three anti-VEGF medications. Aflibercept was compared to bevacizumab and ranibizumab.

**Materials and methods**

**The model**

We developed a two-eye Markov transition model for the calculation of the cost-effectiveness of bevacizumab, ranibizumab and aflibercept. Five health states were chosen based on VA of the better seeing eye as presented in Fig. 17 and in Table 8. The effectiveness of treatment is based on studies that assessed QALY in relation to VA of the better seeing eye of AMD patients (Brown et al. 2000). The transition probabilities of five health states of VA are based on recently published trials (Catt Research Group et al. 2011, Schmidt-Erfurth et al. 2014b). For the transition probabilities see Appendix. Three month cycles were chosen. The health states of the model and their respective utilities are presented in Table 8 (Brown et al. 2000). Health state five with a Snellen VA <0.05 was chosen as the endpoint.

![Fig. 17. The Markov transition model of wet AMD treatment with five health states. Abbreviation: HS = health state.](image)

Direct costs are based on the costs of the Kuopio University Hospital in 2015. In computerized model Microsoft Excel was used. The most recent medicine that entered the market, aflibercept, was used as the reference medicine to which the other two medications were compared.

**Perspective and discounting**

The perspective of this analysis was the hospital perspective. Although this perspective does not take into account the societal costs of treatment, it is the hospital that is the decision maker with respect to the choice of medicine. Furthermore, there is no available reliable up-to-date information about transportation costs or homecare costs of AMD patients in Finland. We applied discounting rates of 0% and 3% per annum.

**Population and population characteristics**

A population of one thousand patients was chosen for the model. The median age of starting wet AMD treatment is 77 years (Brown et al. 2006; Catt Research Group et al. 2011, Dakin et al. 2014) and we can expect that the treatment lasts for the rest of the patient’s life. In Finland, the median life expectancy for men is 82 years and for women 87 years. Therefore, on average we can estimate that the treatment will last for about 7.5 years, which has been rounded up to 8 years. There is a 40% likelihood of developing wet AMD into the fellow eye during a five year period (Solomon et al. 2014), from this we can conclude the average likelihood for each year. With bevacizumab and ranibizumab, it has been shown that the treatment of the first eye does not influence the likelihood of developing wet AMD into the fellow eye (Maguire et al. 2013). It is reasonable to assume that this applies also to aflibercept. Table 2 shows the distribution of visual acuity of the affected eye before the treatment (Catt Research Group et al. 2011). The Snellen VA of the non-affected eye is assumed to be >0.5 (Table 9).

**Costs**

The direct medical costs included in the model were (1) costs of diagnosis including medical visit, fluorescein angiography (FAG) and optical coherence tomography (OCT), (2) costs of the treatment including the medication and

---

**Table 8. The health states of the model and the corresponding QALY-values based on the visual acuity of the better seeing eye.**

<table>
<thead>
<tr>
<th>Definition of the health state</th>
<th>Visual acuity of the better seeing eye (Snellen)</th>
<th>QALY *</th>
</tr>
</thead>
<tbody>
<tr>
<td>HS1 One eye is healthy, the other eye has wAMD, visual acuity is normal.</td>
<td>≥0.5</td>
<td>0.89</td>
</tr>
<tr>
<td>HS2 Both eyes have wAMD; visual acuity is normal.</td>
<td>≥0.5</td>
<td>0.89</td>
</tr>
<tr>
<td>HS3 Both eyes have wAMD and subject has mild visual impairment</td>
<td>&lt;0.5 but ≥0.3</td>
<td>0.81</td>
</tr>
<tr>
<td>HS4 Both eyes have wAMD and subject has low vision</td>
<td>&lt;0.3 but ≥0.05</td>
<td>0.55</td>
</tr>
<tr>
<td>HS5 Both eyes have wAMD and subject is blind</td>
<td>&lt;0.05</td>
<td>0.40</td>
</tr>
</tbody>
</table>

* HS = health state, QALY = quality adjusted life years, wAMD = wet age-related macular degeneration.
* Source: Brown et al. (2000).
the cost of intravitreal injection of the medication, (3) the costs of follow-up including a medical visit and OCT, and (4) rehabilitation of legally blind persons. In Finland, the rehabilitation of legally blind persons is provided mainly by public hospitals and therefore these costs are included in the analysis. The intravitreal injections can cause adverse events such as endophthalmitis, retinal detachment and lens injury. The likelihood of adverse events per each injection is presented in Table 10 and their treatment costs are taken into account in the model. All unit costs are based on costs of the Kuopio University Hospital department of Ophthalmology for 2015 (see Table 11). Furthermore, we calculated the average costs of each 3 month cycle.

### Treatment effect and schedule

We compared treatment protocol of regular injections to one with the pro re nata (PRN) protocol. In the PRN protocol, after three monthly loading injections an injection is given based on the physician’s judgement when the patient visits the clinic as well as the results of OCT. In the regular injection protocol, bevacizumab and ranibizumab are given monthly, but aflibercept is given every other month since this schedule is equally effective (Nguyen et al. 2012). (Nguyen et al. 2012). In clinical trials with a PRN protocol, patients received on average the following number of injections every year; bevacizumab, 7.7 and ranibizumab, 6.9 (Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group et al. 2012). When the patient reached health state five with a Snellen VA of <0.05, no further injections were given.

### Sensitivity analysis

Some of the model parameters were estimations and therefore we performed a sensitivity analysis. In the sensitivity analysis, we increased and decreased the costs of rehabilitation and adverse events by 20%. The life expectancy of people tends to increase, and therefore we also included a 2 year longer period using the same parameters as in the original model.

### Results

The total cost of treatment of 1000 patients, the ICER values based on 0% and 3% discount rates and the number of bilateral wet AMD cases and number of legally blind persons are shown in Table 12. Gaining one additional QALY with aflibercept would cost an additional 1,801,228 euros (3% discount rate) compared to monthly bevacizumab and 3.7 million euros less than treatment with ranibizumab PRN. From the model we could also calculate that aflibercept should cost 128 € per injection in order to be as cost effective as monthly injected bevacizumab. Another option to achieve this would be to administer only 0.98 injections per year per affected eye. In this case, the cost would be the same, whereas the effectiveness would be reduced to some unknown degree. In the sensitivity analysis, a longer time period, 20% change in the costs of legally blind persons’ rehabilitation or AEs treatment did not influence our conclusions (see Table 13).

### Discussion

Bevacizumab is cost efficient in a comparison with aflibercept, which in turn is cost efficient when compared to ranibizumab despite the differences in their treatment protocols. If one examines the total costs, then we can discern the magnitude of the difference between these medications. According to earlier clinical trials, these three medications have similar efficacies and safety profiles (Catt Research Group et al. 2011, Schmidt-Erfurth et al. 2014b). The differences in the cost efficiency are due to differences in price and/or injection intervals.

The strength of our study is the use of a two eye model. There are a number of cost effectiveness studies that have applied a one eye model (or rather the second eye), which assumes that the first eye is already blind. Unfortunately this is not clearly stated in the methods section of these publications and furthermore, this does not reflect the normal clinical setting, since most of the treated patients have only the first eye affected at the initiation of the therapy. Our study would have been fitted from data on patients’ travel and homecare costs.

Elshout et al. (2014) also created a two eye model of AMD treatment with two and five year periods. In their model, bevacizumab was the most cost effective treatment, but with all medication options, the PRN treatment was
superior to monthly injections in contrast to our results. The cost of the procedure of intravitreal injections (321.00€) that they used was very high, which means that every injection was expensive, regardless of which medication was administered. Nowadays the intravitreal injection in Finland is given in the polyclinic instead of an operating theatre. In addition, in some hospitals, the injections are even administered by nurses instead of doctors, which diminishes the costs per injection considerably. It seems that the profession of the person providing the injection does not exert any influence on the adverse events (Simcock et al. 1999; Klaver et al. 2001; Wong et al. 2008, 2014; Kawasaki et al. 2010). The treatment and monitoring of wet AMD have undergone major breakthroughs with the advent of anti-VEGF injections and development of OCT during the past decade. Despite the very active clinical treatment practices and large clinical trials, little is known about the influence of anti-VEGF therapy on the function of the visual pathway. These regular anti-VEGF injections require high resource inputs and therefore the cost-effectiveness of these treatments needs attention.

The publication I with six wet AMD patients showed that VEP amplitude decreased on average by 0.18–0.32 μV and VEP amplitude increased by 1.4–2.0 μV (p < 0.05). In the only previous human study, this kind of VEP change after one bevacizumab injection was not reported (Macky & Mahgoub 2012). These findings indicate the improvement of the function of the visual pathway, but the anatomical location of the improvement cannot be specified with these results. In publications. In clinical practice, this result suggests that VEP might not provide any additional information for the diagnosis or monitoring of wet AMD.

**Conflict of interests**

The authors declare no conflict of interest.

**General Discussion**

**Summary**

Age-related macular degeneration is the leading cause of blindness in the Western world and it has been estimated that AMD causes 8.7% of all blindness worldwide (Mitchell et al. 1995; Klein et al. 1999; Klaver et al. 2001; Wong et al. 2008, 2014; Kawasaki et al. 2010). The treatment and monitoring of wet AMD have undergone major breakthroughs with the advent of anti-VEGF injections and development of OCT during the past decade. Despite the very active clinical treatment practices and large clinical trials, little is known about the influence of anti-VEGF therapy on the function of the visual pathway. These regular anti-VEGF injections require high resource inputs and therefore the cost-effectiveness of these treatments needs attention.

The publication I with six wet AMD patients showed that VEP amplitude and/or latency improved after anti-VEGF injections. In the subsequent study (publication II) with a larger population of 16 patients and six controls, we found that the anti-VEGF injections improved amplitude, but no statistical significant change in latency could be found. In this study, in the treated eyes logMAR visual acuity decreased on average by 0.18 ± 0.32 units (p < 0.05), OCT retinal thickness decreased by 170 ± 200 μm (p < 0.05) and VEP amplitude increased by 1.0 ± 1.4 μV (p < 0.05). In the only previous human study, this kind of VEP change after one bevacizumab injection was not reported (Macky & Mahgoub 2012). These findings indicate the improvement of the function of the visual pathway, but the anatomical location of the improvement cannot be specified with these results. In publication II, we also found a significant correlation between the relative changes of VEP amplitude and retinal thickness \( r = -0.630 \) (p < 0.05). This correlation has not been reported in any previous publications. In clinical practice, this result suggests that VEP might not provide any additional information for the diagnosis or monitoring of wet AMD.

**Table 12.** Total costs and accumulated QALYs over an eight year time span per 1000 patients.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total costs (€)</th>
<th>ICER (€/QALY)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0% discount rate</td>
<td>3% discount rate</td>
<td>QALYs</td>
</tr>
<tr>
<td>Afiblercept</td>
<td>45 269 777</td>
<td>39 921 295</td>
<td>6888</td>
</tr>
<tr>
<td>Bevacizumab PRN</td>
<td>10 448 952</td>
<td>9 219 224</td>
<td>6870</td>
</tr>
<tr>
<td>Bevacizumab PRN</td>
<td>18 964 725</td>
<td>16 783 679</td>
<td>6862</td>
</tr>
<tr>
<td>Ranibizumab PRN</td>
<td>167 128 430</td>
<td>147 321 659</td>
<td>6880</td>
</tr>
<tr>
<td>Total costs (€)</td>
<td>10 871 502</td>
<td>9 504 554</td>
<td>6873</td>
</tr>
</tbody>
</table>

ICER = incremental cost effective ratio, PRN = pro re nata, QALY = quality adjusted life year, wAMD = wet age related macular degeneration.

**Table 13.** ICER values of the sensitivity analysis.

<table>
<thead>
<tr>
<th>Medication</th>
<th>0% discount rate</th>
<th>3% discount rate</th>
<th>5% discount rate</th>
<th>10% discount rate</th>
<th>20% discount rate</th>
<th>The cost of rehabilitation of legally blind persons (€)</th>
<th>The cost of adverse event (€)</th>
<th>Ten years time period (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 036 594</td>
<td>2 041 102</td>
<td>2 034 933</td>
<td>2 042 763</td>
<td>1 482 076</td>
<td>2 036 594</td>
<td>2 041 102</td>
<td>2 034 933</td>
</tr>
<tr>
<td>Bevacizumab PRN</td>
<td>1 050 597</td>
<td>1 053 971</td>
<td>1 050 723</td>
<td>1 053 845</td>
<td>798 611</td>
<td>1 050 597</td>
<td>1 053 971</td>
<td>1 050 723</td>
</tr>
<tr>
<td></td>
<td>1 799 282</td>
<td>1 803 174</td>
<td>1 797 777</td>
<td>1 804 679</td>
<td>1 294 057</td>
<td>1 799 282</td>
<td>1 803 174</td>
<td>1 797 777</td>
</tr>
<tr>
<td>Bevacizumab PRN</td>
<td>926 855</td>
<td>929 495</td>
<td>926 664</td>
<td>929 416</td>
<td>695 979</td>
<td>926 855</td>
<td>929 495</td>
<td>926 664</td>
</tr>
</tbody>
</table>

ICER = incremental cost effective ratio, PRN = pro re nata.
AMD patients. Nonetheless, VEP might offer an objective tool to verify the functional recovery of the visual system.

In the publication III using binocular stimulation the face-specific N170 component was pronounced in all subjects with longer peak latencies in wet AMD patients than in controls (170 ± 13 versus 155 ± 14, p = 0.032). In patients and controls, a deviance-related negativity (DRN) reflecting an early prediction of perceiving a face was present. Visual acuity of the affected eye improved in patients from logMAR 0.71 (±0.33) to 0.52 (±0.39) by 119 (±23) days, but no simultaneous change in face-specific electrical potentials were presented. There are no previous publications on face detection VEP nor its change after the anti-VEGF injections. Our findings are congruent with the reports stating that the quality of life (QALY) and the ability to perform the activities of daily living are largely influenced only by the VA of the better seeing eye (Brown 1999; McClure et al. 2000).

In publication IV a two-eye Markov transition model was developed to analyse the cost-effectiveness of the aflibercept, bevacizumab and ranibizumab injections of wet AMD treatment. The need for the two-eye model was encouraged by the finding of publication III, since a one-eye model would not reflect the everyday situation of the patients i.e. the disease exerts only a low influence on face detection if there is only one affected eye. Bevacizumab was the most cost-effective treatment for wet AMD despite the treatment protocol. In comparison to recent cost-effectiveness analysis of the three anti-VEGF injections (Elshout et al. 2014), the order of the different medications cost-effectiveness was the same, but in the present study regular monthly injection of bevacizumab was the most-effective treatment modality in contrast to PRN, which was superior in the study of Elshout et al. (2014).

Limitations of the present studies

This study was a pilot study on neurophysiological changes of wet AMD patients after the anti-VEGF treatment. In the publications I-III, there were some limitations due to the study design since it was a prospective interventional cohort study. The number of patients and length of follow-up period in these neurophysiological studies were limited. During this short follow-up period not all the neural function might be recovered though the retinal thickness improved, i.e. the functional and anatomical improvement might not happen simultaneously. Repeated VEPs might reveal the functional recovery sequence. The publications I-III were pilot studies on this field and further prospective controlled studies with larger number of subjects and longer follow-up period should be conducted to confirm the present results. Also the larger number of subjects could allow the analysis of different wet AMD subgroups, since our study population was too limited to apply this approach.

No kind of binding of the investigators was performed, but in practice the data was analysed as if the researchers were blinded since the clinical data was collected by a single researcher (PV) and the VEPs were performed and analysed by another researcher (AP) and only thereafter was the data merged. However, the researchers knew which eye was treated and which of the patients served as controls. The blinding was thought to be unnecessary, since there was only one treatment option used and the patients knew that they received the treatment. In addition, the controls knew that they were healthy volunteers.

In the publication II in the control group both eyes were used as control eyes, which might somewhat deviate the results since the results of the same individual are likely to correlate. Although it has to be noted that the results of control patients are only analysed by comparing the base and follow-up results and the results are not compared between patients and controls. The idea of the control group was rather to test the repeatability of VEP methodology.

The technical development of the OCT equipment has been relatively fast. In this study, the used OCT device changed during the study period from Spectral OCT/SLO, Ophthamlic Technologies Inc., Toronto, Canada to Spectrals Heidelberg Engineering, Heidelberg, Germany, but this was not assumed to influence the results of the retinal thickness measurement. It has to be noted, that each individual patient was monitored with the same OCT device. In studies performed with healthy subjects, there seems to be a difference between the devices when automated retinal thickness measurement is used (Wolf-Schnurrbusch et al. 2009), but at least partially that is caused by different retinal segmentation borders. In this study, this source of errors was avoided by manual corrections.

In the publication IV a cost-effectiveness model was constructed. As is generally the case, these experiments are always a simplification of true reality, since they cannot take all details into account. The calculations are often based on previous clinical trials and this leads to some limitations to the interpretation of the results. The transition probabilities used in the cost-effectiveness study were collected from large clinical trials with strict enrolment criteria. In everyday clinical practice, the transition probabilities might be somewhat different. In this study, a hospital perspective was chosen instead of a social perspective, mainly because no reliable information was available on travel costs in Finland. This might have some influence on the results since aflibercept injections and therefore hospital visits are less frequent compared to the other medications. Furthermore, the treatment options are becoming more complicated with individual options of treat-and-extend protocol and possibility to change the anti-VEGF medication in the case of non-responders. At the moment, no clear indications seem to exist to help the clinician to decide when another anti-VEGF medication should be tried. The TER could not have been analysed as an option in the cost-effectiveness study since there is a lack of randomized controlled clinical trials, which have applied this injection protocol.

**Future directions**

**AMD treatment**

Even after the large clinical trials, there is no clear consensus on how wet AMD should be managed with anti-VEGF injections. There are several issues that need further clarification. The TER should be evaluated in comparison to monthly injections and PRN protocol in a large prospective controlled randomized clinical trial. The change of anti-VEGF medication might be beneficial in the resistant cases, but it is not clear what are the signs that indicate that a change is needed and when should the change be done (Cho et al. 2013; Singh et al. 2015). A combination
therapy of anti-VEGFs and E10030 anti-platelet derived growth factor (Fovista®, Ophthotech, New York, NY) or anti-complement factor C5 (Zimura®, Ophthotech, New York, NY) are under phase 2 clinical trials (Drolet et al. 2016; Jaffe et al. 2016). The potential benefits of these products in the clinic are still not known. An intravitreal dexamethasone implant (Ozurdex®, Allergan, Irvine, California, USA) in combination with an anti-VEGF preparation has been tested in small populations with promising results, but further studies will be needed (Calvo et al. 2015; Vakalis et al. 2015). A combination of anti-VEGF injection and PDT could be an option, at least in some special cases (Wang et al. 2014). New treatment methods such as intraocular gene therapy could save the resources involved in long-term intravitreal therapy and stabilize or even cure the disease, but to date, this kind of treatment is only theoretical and far from a reality (Kinnunen & Yli-Herttuala 2012b). Stem cell therapy may be also an option in the future (Schwartz et al. 2015). For people blinded by advanced AMD, some kind of retinal prosthesis may help with their orientation, even if they are not able to restore normal vision (Stingl et al. 2010; Zrenner et al. 2011; Välimäki 2012).

It has been shown that the results of the treatment are dependent on when the treatment is initiated, i.e. it should start as soon as the diagnosis has been made (Rasmussen et al. 2015). This may favour regular screening of the entire over 65 years old population, but with current technical options, screening it is not cost-effective (Castillo et al. 2014). Surprisingly, low vision screening at the primary health care, has not been shown to improve the vision of wet AMD patients (Chou et al. 2016). In Japan, the screening of wet AMD has been shown to be effective in reducing blindness, but it is not cost-effective (Tamura et al. 2015). When the analysis of genes and inheritance mapping becomes routine, perhaps it will be possible to identify the high-risk individuals and monitor them more closely in order to start the medication immediately when the signs of wet AMD are detected.

Further neurophysiological studies

Due to the limitations of the publications I-III further neurophysiological studies with VEP and VER techniques are required to clarify these preliminary promising results. This would involve larger patients groups and longer follow-up period at least up to six months.

With the pattern-ERG, the function of the retinal ganglion cells and their axons locally at the macula regions can be more specifically evaluated, which could aid in the diagnosis and follow-up of the functional recovery of the retinal part of the optic nerve fibres. In the development of wet AMD, inflammation plays a role and oedema can cause problems with the homeostasis of the affected cells as well as demyelination of the nerve fibres, so that their function, which is associated with VA, might not recover simultaneously with the anatomical changes, detected by the OCT. Thus, a more detailed analysis of the disease and its response to the treatment could be achieved in the future trials by a combination of a neurophysiological tests capable of evaluating the visual system from the retina up to the visual cortical areas.

Functional MRI offers an interesting tool to investigate the neurophysiological changes after the anti-VEGF injections. Individual patient investigations using functional MRI analysis have examined the reorganization of the visual cortex occurring after AMD (Baker et al. 2008; Dilks et al. 2009, 2014). It seems that large-scale reorganization of visual processing occurs only after complete absence of functional foveal vision. On the contrary, another study has also concluded that there is no remapping of visual cortex due to AMD (Baseler et al. 2011b). There is a case report where fMRI was conducted in an anti-VEGF treated wet AMD patient; this suggested that the activated area of the visual cortex increased after the anti-VEGF injections (Baseler et al. 2011a). Larger scale studies will need to be conducted to confirm this finding.

Cost-effectiveness of treatment and follow-up of AMD-patients

There are a number of potential ways to decrease the costs of intravitreal injections. In study II, we detected a correlation between VA and retinal thickness measured on OCT. Based on this finding, one could speculate that in the future, the monitoring of wet AMD treatment could be done solely based on objective OCT findings which can be done rapidly. This would reduce the costs of follow-up. The automated detection of active wet AMD by OCT could further reduce the costs of follow-up (Chakravarthy et al. 2016). The costs of injections are also elevated by the need for a skilled workforce. The current clinical practice is that the intravitreal injections are mainly administered by physicians. It has been shown that injections delivered by nurses are not associated with an increase in the number of complications (Hasler et al. 2015), and could be more cost-effective.

 Nowadays individualized treatment is being utilized in the TER approach (Stewart 2015). It is likely that more optimal results could be achieved with more individualized treatment protocols incorporating several treatment options. At the present time, we have few examples of these possibilities. In treatment-resistant wet AMD cases, when bevacizumab or ranibizumab do not result in a good therapeutic response, aflibercept might improve anatomical structures and improve BCVA (Chang et al. 2014; Singh et al. 2014, 2015). It is possible that genetic mapping might be able identify the non-responders to certain anti-VEGF preparations at an early stage as well as those cases needing more frequent or combined treatment. The combination treatment of PDT and ranibizumab has been shown to be equally effective as a sole ranibizumab treatment, even though the visual outcome might be better with monotherapy of ranibizumab (Si et al. 2014; Hatz et al. 2015). In patients with high risk of an atherosclerotic complication or stroke, the combination therapy of PDT and anti-VEGF injection might be the treatment of choice. The combination might also be an option for a patient reluctant to be subjected to the stress of repeated intravitreal injections. In the future, individualized treatment could be extended i.e. the creation of personal treatment protocol, which could take into account the non-responding to certain anti-VEGF, the risks of systemic adverse events and patient’s commitment to the treatment. The biomarkers obtained via OCT can further guide the individual treatment modalities including angiographic OCT and Doppler OCT (Schmidt-Erfurth & Waldstein 2016).

In the CEA of ophthalmic diseases affecting both eyes, the author recommends that a two-eye model should be
adopted. This type of model can incorporate both eyes in the analysis whether or not both eyes are treated. This is important since in the diseases affecting the central vision, only the VA of the better seeing eye exerts an influence on the HRQoL (Hirniss 2014).

Cost-effectiveness and ethics of AMD treatment
Our findings from the face detection task support the HRQoL studies (e.g. Hirniss 2014), which raises ethical questions concerning the treatment of the first affected eye. In our short term follow-up, the treatment of the first affected eye does not seem to improve the face detection, but this will need to be clarified with longer follow-up. Based on earlier studies VA of the worse eye has only a minor impact on QALY. Therefore, the treatment of first affected eye is associated with high costs, but provides only limited benefits in terms of QALYs. Should we choose not to treat the first affected eye? The physician’s Hippocratic Oath obliges the doctors to heal his/her patient. Who would be held responsible in a case when a patient loses vision in the better seeing but still untreated eye, for example by trauma, vein occlusion or uveitis? On ethical grounds, we have to treat the first affected eye despite the costs and minimal influence on the QALYs and also take into account the patient’s wishes. There is a report suggesting improvement of visual function regardless of whether the treated eye was the better- or worse-seeing eye (Bressler et al. 2010).

From a societal perspective, the main aim of wet AMD treatment is to reduce the numbers of legally blind persons. From the individual patient’s point of view, the quality of life becomes dramatically diminished when the Snellen VA of better-seeing eye declines below 0.3 (Brown et al. 2000). In Finland, the median age of legal blind wet AMD patients has increased from 77 years of age in the year 2000 to a current value of 80 years, highlighting the importance and benefits of treatment of wet AMD (Ojamo 2016).

Conclusions
1 In wet AMD VEP is abnormal. The anti-VEGF treatment of wet AMD patients exerts an effect on the neurophysiological responses. VEP amplitudes appear to increase after treatment, suggesting that there is improved visual processing.
2 In treated wet AMD patients, the improvement in visual acuity and the increase in VEP amplitude are associated with a decrease in retinal thickness as measured by OCT. However, there is no evidence from short term follow-up that VEP confers added value in the diagnosis or monitoring of wet AMD.
3 Monocular wet AMD clearly influenced face-specific brain electrophysiological components. However, our wet AMD patients had not lost their binocular face detection ability. This supports the view that only the vision of the better seeing eye has a marked influence on every-day life.
4 In the cost-effectiveness analysis of wet AMD treatment, monthly injected bevacizumab is the most cost effective treatment and; monthly treatment with ranibizumab being the least cost effective.

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Appendix

The transition probabilities of 3 months period between the health state of aflibercept, bevacizumab and ranibizumab according to different treatment protocols.

<table>
<thead>
<tr>
<th>Health State</th>
<th>Aflibercept*</th>
<th>Bevacizumab monthly†</th>
<th>Bevacizumab PRN†</th>
<th>Ranibizumab monthly†</th>
<th>Ranibizumab PRN†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>To</td>
<td>From HS1</td>
<td>HS2</td>
<td>HS3</td>
<td>HS4</td>
</tr>
<tr>
<td>HS1</td>
<td>0.979</td>
<td>0.008</td>
<td>0.008</td>
<td>0.006</td>
<td>0.000</td>
</tr>
<tr>
<td>HS2</td>
<td>0.000</td>
<td>0.993</td>
<td>0.005</td>
<td>0.002</td>
<td>0.000</td>
</tr>
<tr>
<td>HS3</td>
<td>0.000</td>
<td>0.048</td>
<td>0.942</td>
<td>0.010</td>
<td>0.000</td>
</tr>
<tr>
<td>HS4</td>
<td>0.000</td>
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</tr>
</tbody>
</table>

HS = health state, PRN = pro re nata.
Sources: *Schmidt-Erfurth et al. (2014b), †Catt Research Group et al. (2011).

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