
Evidence summaries for the Finnish Current Care Guideline Wet Age-Related Macular Degeneration

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nak08685

Fluorescein angiography (FA) in the diagnosis of wet AMD

30.3.2016

Tanja Laukkala

Level of evidence = C**Fluorescein angiography (FA) may be regarded as the gold standard in the diagnosis of wAMD when it is not contraindicated.**

The aim of the systematic review [R1] was to determine the optimal role of optical coherence tomography (OCT) in diagnosing people newly presenting with suspected neovascular age-related macular degeneration (nAMD) and in monitoring those previously diagnosed with the disease.

Electronic databases searched included MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Bioscience Information Service, Science Citation Index, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Medion, Health Technology Assessment database, PsycINFO, Applied Social Sciences Index and Abstracts, conference abstracts from the American Academy of Ophthalmology, the Association for Research in Vision and Ophthalmology, the European Association for Vision and Eye Research and current research registers. Searches were carried out from 1995 to March 2013 other than for conference abstracts (2009 to November 2012).

Types of studies considered included direct or indirect comparisons reporting diagnostic outcomes. The population was people with newly suspected nAMD or those previously diagnosed with the disease and under surveillance monitoring. The index test was TD-OCT or SD-OCT and comparator tests considered were clinical evaluation, visual acuity (VA), Amsler grid, colour fundus photographs, infrared reflectance, red-free images or blue reflectance, fundus autofluorescence (FAF) imaging, indocyanine green angiography (ICGA), preferential hyperacuity perimetry (PHP) and microperimetry. The reference standard was FA. Two reviewers independently screened the titles and abstracts of all reports identified by the search strategy and full-text papers were obtained for assessment. Data extraction was undertaken by one reviewer and checked by a second. Two reviewers independently assessed the risk of bias of the studies using the quality assessment of diagnostic accuracy studies, version 2 instrument.

Altogether 22 diagnostic studies with 2124 patients were included in the systematic review. 21 studies reported eyes as an unit of analysis (number of eyes 1754) and one study reported that 155 patients were included. 45.4% (N=742) were male. Age: median 76.0 years (range 51.4–84.6).

Tests reported in the included diagnostic studies; OCT 13 studies (N=1335); TS –OCT 12 studies and SD-OCT 1 (N=19), ICGA 8 studies (N=458), PHP three studies (N=491) and FP (N=185), Amsler grid (N=98) and FAF one study (N=62).

Four studies, all TD-OCT, reported both sensitivity and specificity, providing sufficient data for inclusion in a meta-analysis. The pooled sensitivity and specificity (95%CI) was 88% (46% to 98%) and 78% (64% to 88%). LR+ was 4.08 (95% confidence interval 2.37 to 7.04), LR - 0.15 (95% confidence interval 0.02 - 0.98) and DOR 26.86 (95% confidence interval 3.36- 214.81).

In descriptive analyses, median sensitivity was high for ICGA (93.2%, range 84.6–100.0%; four studies) and FAF (93.3%; one study), followed by PHP (81.5%, range 50.0–84.8%; three studies), colour fundus photography (70.0%; one study) and lowest for Amsler grid (41.7%; one study). Specificity was highest for colour fundus photography (95%; one study), followed by PHP (84.6% and 87.7%; two studies), and was low for FAF (37.1%; one study) and ICGA (36.8%; one study).

- Study quality: High
- Applicability: Good

Comment: There was heterogeneity among the primary studies included in the review. Selection of the patients may have caused bias.

The aim of this HTA report written in German with an English abstract [R2] was to investigate the efficacy as well as (economic) efficiency of OCT compared to FA in the diagnostics of AMD. A systematic literature search was performed in 34 international databases which yielded 2324 articles. Following a two-part selection process according to predefined selection criteria only eight medical publications remained for inclusion for assessment. According to the defined criteria the quality of the studies was low except for one study. The number of investigated patients was below 35 in four publications, between 35 and 61 in three studies, and above 100 in only one publication. The study with the highest quality evaluated the diagnostic accuracy of OCT compared to FA in 131 eyes of 118 patients suspected of having choroidal neovascularisation. For OCT the sensitivity for detecting new potentially treatable lesions (84 eyes with classic or occult choroidal neovascularisation or serous pigment epithelial detachment) was 96% and the specificity was 66%. Including stereo colour images led to a sensitivity of 94% and a specificity of 89%. The authors conclude that OCT cannot replace the gold standard FA during the primary diagnostic procedure. OCT yields diagnostic findings in addition to FA results, unclear findings of FA can be clarified and in certain cases OCT can possibly replace FA. No recommendation was made from the economic point of view, as no economic assessments were available. In the studies published so far older

models of OCT had been used and using newer models might change the findings for some classes or stages of AMD.

- Study quality: Low
- Applicability: Good

Comment: Assessment of quality is based on the English abstract of the HTA-rapport.

According to European Society of Retina Specialists (EURETINA) guideline [\[R3\]](#) fluorescein angiography (FA) is the only diagnostic examination that can confirm the mere existence of a CNV and if not contraindicated for systemic risks is routinely mandatory.

- Study quality: Moderate
- Applicability: Good

The aim of this retrospective UK study was to evaluate the diagnostic accuracy of spectral-domain optical coherence tomography (SD-OCT) for neovascular age-related macular degeneration, nAMD [\[R4\]](#). A retrospective review of all SD-OCT, colour fundus photographs (FP) and fundus fluorescein angiography (FA) of 411 consecutive patients (822) eyes that were referred to rapid access Macular Clinic from February 2009 to February 2013. Inclusion criteria were all patients over 50 years of age that were referred for suspected nAMD by optometrists, general practitioners or other ophthalmologists and had symptoms of reduced vision, metamorphopsia, or signs suggestive of nAMD as determined by referring clinician. Also patients who may have had treatment 6 or more months previously with verteporfin photodynamic therapy or antiVEGF but were thought to have new CNV lesions were included. A small number of individuals may have been myopic and these were not excluded from the analysis. Exclusion criteria included all patients that had either no SD-OCT or FP/FA available for analysis or those patients where one imaging modality was deemed ungradable. In addition, if the SD-OCT or FA were not performed within 7 days of each other the patient was excluded. Patients with CNV secondary to angioid streaks or evidence of chorioretinitis were excluded.

278 eyes were graded as having CNV with OCT, and had both gradable FA and SD-OCT. Within this group the mean age was 80.6 years (range 51–97) and 115 were male and 163 female. All SD-OCT images were graded by at least two ophthalmologists and if there was disagreement then adjudication by a third ophthalmologist took place. After the assignment of the SD-OCT grade the patient's mydriatic colour FP was reviewed. FA images were graded as classic, predominantly classic, minimally classic, occult, disciform scar, peripapillary CNV, no CNV, or other pathology. CNV was considered present if classic or occult leakage was detected. With SD-OCT CNV was

considered present with the grading of changes at the level of inner choroid the RPE or retina, also shown by pictures in the study. There were a total of 47 false positives with SD-OCT (16.9%), seven of these were diagnosed as disciform scars (inactive chronic CNV scars). Reference to FP did not change any of SD-OCT grades. One false negative was present. The sensitivity and specificity of SD-OCT alone for detecting CNV was 100% and 80.8%. The authors conclude that SD-OCT is highly sensitive in detecting nAMD but specificity and false-positive rates compared to FA are currently unacceptable.

- Study quality: Low
- Applicability: Good

References

R1=Mowatt G, Hernández R, Castillo M ym. Optical coherence tomography for the diagnosis, monitoring and guiding of treatment for neovascular age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess* 2014;18:1-254 [PubMed](#)

R2=Stürzlinger H, Genser D, Fröschl B. Evaluation of optical coherence tomography in the diagnosis of age related macula degeneration compared with fluorescence angiography. *GMS Health Technol Assess* 2007;3:Doc02 [PubMed](#)

R3=Schmidt-Erfurth U, Chong V, Loewenstein A ym. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *Br J Ophthalmol* 2014;98:1144-67 [PubMed](#)

R4=Wilde C, Patel M, Lakshmanan A ym. The diagnostic accuracy of spectral-domain optical coherence tomography for neovascular age-related macular degeneration: a comparison with fundus fluorescein angiography. *Eye (Lond)* 2015;29:602-9; quiz 610 [PubMed](#)

nak08686

Optical coherence tomography (OCT) in the diagnosis of wet AMD

30.3.2016

Tanja Laukkala

Level of evidence = C

Optical coherence tomography (OCT) may be sensitive but not accurate enough to be used as the only examination method in the diagnosis of wAMD.

The aim of the systematic review [R1] was to determine the optimal role of optical coherence tomography (OCT) in diagnosing people newly presenting with suspected neovascular age-related macular degeneration (nAMD) and in monitoring those previously diagnosed with the disease.

Electronic databases searched included MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Bioscience Information Service, Science Citation Index, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Medion, Health Technology Assessment database, PsycINFO, Applied Social Sciences Index and Abstracts, conference abstracts from the American Academy of Ophthalmology, the Association for Research in Vision and Ophthalmology, the European Association for Vision and Eye Research and current research registers. Searches were carried out from 1995 to March 2013 other than for conference abstracts (2009 to November 2012).

Types of studies considered included direct or indirect comparisons reporting diagnostic outcomes. The population was people with newly suspected nAMD or those previously diagnosed with the disease and under surveillance monitoring. The index test was TD-OCT or SD-OCT and comparator tests considered were clinical evaluation, visual acuity (VA), Amsler grid, colour fundus photographs, infrared reflectance, red-free images or blue reflectance, fundus autofluorescence (FAF) imaging, indocyanine green angiography (ICGA), preferential hyperacuity perimetry (PHP) and microperimetry. The reference standard was FA. Two reviewers independently screened the titles and abstracts of all reports identified by the search strategy and full-text papers were obtained for assessment. Data extraction was undertaken by one reviewer and checked by a second. Two reviewers independently assessed the risk of bias of the studies using the quality assessment of diagnostic accuracy studies, version 2 instrument.

Altogether 22 diagnostic studies with 2124 patients were included in the systematic review. 21 studies reported eyes as an unit of analysis (number of eyes 1754) and one study reported that 155 patients were included. 45.4% (N=742) were male. Age: median 76.0 years (range 51.4–84.6).

Tests reported in the included diagnostic studies; OCT 13 studies (N=1335); TS-OCT 12 studies and SD-OCT 1 (N=19), ICGA 8 studies (N=458), PHP three studies (N=491) and FP (N=185), Amsler grid (N=98) and FAF one study (N=62).

Four studies, all TD-OCT, reported both sensitivity and specificity, providing sufficient data for inclusion in a meta-analysis. The pooled sensitivity and specificity (95% CI) was 88% (46% to 98%) and 78% (64% to 88%). LR+ was 4.08 (95% confidence interval 2.37 to 7.04), LR - 0.15 (95% confidence interval 0.02 - 0.98) and DOR 26.86 (95% confidence interval 3.36-214.81).

In descriptive analyses, median sensitivity was high for ICGA (93.2%, range 84.6–100.0%; four studies) and FAF (93.3%; one study), followed by PHP (81.5%, range 50.0–84.8%; three studies), colour fundus photography (70.0%; one study) and lowest for Amsler grid (41.7%; one study). Specificity was highest for colour fundus photography (95%; one study), followed by PHP (84.6% and 87.7%; two studies), and was low for FAF (37.1%; one study) and ICGA (36.8%; one study).

- Study quality: High
- Applicability: Good

Comment: There was heterogeneity among the primary studies. Patient selection may have caused risk of bias.

The purpose of this systematic review and meta-analysis [R2] was to study the diagnostic performance of optical coherence tomography (OCT) and alternative diagnostic tests for neovascular age-related macular degeneration (nAMD). The index test was OCT including time-domain (TD-OCT) and spectral domain (SD-OCT); comparator tests: visual acuity, clinical evaluation (slit lamp), Amslergrid, colour fundus photographs, infra-red reflectance, red-free images/blue reflectance, fundus autofluorescence imaging (FAF), indocyanine green angiography (ICGA), preferential hyperacuity perimetry (PHP), and microperimetry; reference standard: fundus fluorescein angiography. Databases searched included MEDLINE, MEDLINE In Process, EMBASE, Biosis, SCI, the Cochrane Library, DARE, MEDION, and HTA database. Last literature searches: March 2013. Risk of bias assessed using QUADAS-2. Meta-analysis models were fitted using hierarchical summary receiver operating characteristic (HSROC) curves. Twenty-two studies (2 abstracts and 20 articles) enrolling 2124 participants were identified, reporting TD-OCT (12 studies), SD-OCT (1 study), ICGA (8 studies), PHP (3 studies), Amsler grid, colour fundus photography and FAF (1 study each). Most studies were considered to have a high risk of bias in the patient selection (55%, 11/20), and flow and timing (40%, 8/20) domains. In a meta-analysis of TD-OCT studies, sensitivity and specificity (95% CI) were 88% (46–98%) and 78% (64–88%). There was insufficient information to undertake meta-analysis for other tests. The authors conclude

that TD-OCT is a sensitive test for detecting nAMD, although specificity was only moderate. Data on SD-OCT are sparse. Diagnosis of nAMD should not rely solely on OCT.

- Study quality: High
- Applicability: Good

Comment: Systematic review and meta-analysis is based on the same literature search than the previous study [\[R1\]](#).

The aim of this retrospective UK study was to evaluate the diagnostic accuracy of spectral-domain optical coherence tomography (SD-OCT) for neovascular age-related macular degeneration, nAMD [\[R3\]](#). A retrospective review of all SD-OCT, colour fundus photographs (FP) and fundus fluorescein angiography (FA) of 411 consecutive patients (822) eyes that were referred to rapid access Macular Clinic from February 2009 to February 2013. Inclusion criteria were all patients over 50 years of age that were referred for suspected nAMD by optometrists, general practitioners or other ophthalmologists and had symptoms of reduced vision, metamorphopsia, or signs suggestive of nAMD as determined by referring clinician. Also patients who may have had treatment 6 or more months previously with verteporfin photodynamic therapy or antiVEGF but were thought to have new CNV lesions were included. A small number of individuals may have been myopic and these were not excluded from the analysis. Exclusion criteria included all patients that had either no SD-OCT or FP/FA available for analysis or those patients where one imaging modality was deemed ungradable. In addition, if the SD-OCT or FA were not performed within 7 days of each other the patient was excluded. Patients with CNV secondary to angioid streaks or evidence of chorioretinitis were excluded.

278 eyes were graded as having CNV with OCT, and had both gradable FA and SD-OCT. Within this group the mean age was 80.6 years (range 51–97) and 115 were male and 163 female. All SD-OCT images were graded by at least two ophthalmologists and if there was disagreement then adjudication by a third ophthalmologist took place. After the assignment of the SD-OCT grade the patient's mydriatic colour FP was reviewed. FA images were graded as classic, predominantly classic, minimally classic, occult, disciform scar, peripapillary CNV, no CNV, or other pathology. CNV was considered present if classic or occult leakage was detected. With SD-OCT CNV was considered present with the grading of changes at the level of inner choroid the RPE or retina, also shown by pictures in the study. There were a total of 47 false positives with SD-OCT (16.9%), seven of these were diagnosed as disciform scars (inactive chronic CNV scars). Reference to FP did not change any of SD-OCT grades. One false negative was present. The sensitivity and specificity of SD-OCT alone for detecting CNV was 100% and 80.8%. The authors conclude that SD-

OCT is highly sensitive in detecting nAMD but specificity and false-positive rates compared to FA are currently unacceptable.

- Study quality: Poor
- Applicability: Good

References

R1=Mowatt G, Hernández R, Castillo M ym. Optical coherence tomography for the diagnosis, monitoring and guiding of treatment for neovascular age-related macular degeneration: a systematic review and economic evaluation. Health Technol Assess 2014;18:1-254 [PubMed](#)

R2=Castillo MM, Mowatt G, Lois N ym. Optical coherence tomography for the diagnosis of neovascular age-related macular degeneration: a systematic review. Eye (Lond) 2014;28:1399-406 [PubMed](#)

R3=Wilde C, Patel M, Lakshmanan A ym. The diagnostic accuracy of spectral-domain optical coherence tomography for neovascular age-related macular degeneration: a comparison with fundus fluorescein angiography. Eye (Lond) 2015;29:602-9; quiz 610 [PubMed](#)

nak08687

Indocyanine green angiography (ICGA) in the diagnosis of wet AMD

30.3.2016

Tanja Laukkala

Level of evidence = C**Indocyanine green angiography (ICGA) may be suitable as a complementary method in the diagnostics of wAMD.**

The aim of the systematic review [R1] was to determine the optimal role of optical coherence tomography (OCT) in diagnosing people newly presenting with suspected neovascular age-related macular degeneration (nAMD) and in monitoring those previously diagnosed with the disease.

Electronic databases searched included MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Bioscience Information Service, Science Citation Index, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Medion, Health Technology Assessment database, PsycINFO, Applied Social Sciences Index and Abstracts, conference abstracts from the American Academy of Ophthalmology, the Association for Research in Vision and Ophthalmology, the European Association for Vision and Eye Research and current research registers. Searches were carried out from 1995 to March 2013 other than for conference abstracts (2009 to November 2012).

Types of studies considered included direct or indirect comparisons reporting diagnostic outcomes. The population was people with newly suspected nAMD or those previously diagnosed with the disease and under surveillance monitoring. The index test was TD-OCT or SD-OCT and comparator tests considered were clinical evaluation, visual acuity (VA), Amsler grid, colour fundus photographs, infrared reflectance, red-free images or blue reflectance, fundus autofluorescence (FAF) imaging, indocyanine green angiography (ICGA), preferential hyperacuity perimetry (PHP) and microperimetry. The reference standard was FA. Two reviewers independently screened the titles and abstracts of all reports identified by the search strategy and full-text papers were obtained for assessment. Data extraction was undertaken by one reviewer and checked by a second. Two reviewers independently assessed the risk of bias of the studies using the quality assessment of diagnostic accuracy studies, version 2 instrument.

Altogether 22 diagnostic studies with 2124 patients were included in the systematic review. 21 studies reported eyes as an unit of analysis (number of eyes 1754) and one study reported that 155 patients were included. 45.4% (N=742) were male. Age: median 76.0 years (range 51.4–84.6).

Tests reported in the included diagnostic studies; OCT 13 studies (N=1335); TS –OCT 12 studies and SD-OCT 1 (N=19), ICGA 8 studies (N=458), PHP three studies (N=491) and FP (N=185), Amsler grid (N=98) and FAF one study (N=62).

Four studies, all TD-OCT, reported both sensitivity and specificity, providing sufficient data for inclusion in a meta-analysis. The pooled sensitivity and specificity (95% CI) was 88% (46% to 98%) and 78% (64% to 88%). LR+ was 4.08 (95% confidence interval 2.37 to 7.04), LR - 0.15 (95% confidence interval 0.02 - 0.98) and DOR 26.86 (95% confidence interval 3.36- 214.81).

In descriptive analyses, median sensitivity was high for ICGA (93.2%, range 84.6–100.0%; four studies) and FAF (93.3%; one study), followed by PHP (81.5%, range 50.0–84.8%; three studies), colour fundus photography (70.0%; one study) and lowest for Amsler grid (41.7%; one study). Specificity was highest for colour fundus photography (95%; one study), followed by PHP (84.6% and 87.7%; two studies), and was low for FAF (37.1%; one study) and ICGA (36.8%; one study).

- Study quality: High
- Applicability: Good

Comment: There was heterogeneity among the studies included in the reviews. Patient selection may have caused risk of bias.

Consecutive angiographic records of 52 patients with unilateral wet AMD in one eye and drusen in fellow eye undergoing both FA and ICGA were retrospectively reviewed to assess the contribution of ICGA to FA in this patient group [R2]. Inclusion criteria were as follows; age 50 years or older, wet AMD in one eye, drusen without clinical or fluorescein angiographic evidence of CNV in the fellow eye, clear ocular media, no other retinal disease. Exclusion criteria were as follows; fluorescein angiograms with findings suspicious for CNV due to AMD, other retinal diseases and eyes with geographic atrophy. Drusen were graded according to clinical appearance to low, moderate or high severity. The primary outcome measure was an abnormal hyperfluorescence on ICGA not observed on FA of drusen eyes. Fifty-two pairs of eyes met inclusion criteria and were included into study. Twenty-four (46.2%) patients were men. The mean age of the patients was 76.9 8.2 years (range 63-92). 50 of 52 demonstrated no leakage on both FA and ICGA. ICGA leakage was observed in 20% (2 out of 10) eyes of high severity drusen group, which was not observed on FA. The authors conclude that in eyes of drusen with high grade severity, ICGA enhanced imaging of occult CNV not observed by FA.

- Study quality: Poor
- Applicability: Good

An Austrian study [R3] was included in the systematic review [R1]. The aim of the study was to evaluate the diagnostic characteristics of type 2 (classic) choroidal neovascularizations secondary to age-related macular degeneration using spectral domain-optical coherence tomography (SD OCT), indocyanine green angiography (ICGA), and fluorescein angiography (FA). Fifty-three consecutive patients who consulted the clinic at the department of Ophthalmology years 2008-2009 were screened for inclusion and 13 eyes were included in this study. The inclusion criteria were type 2 CNV defined as an area of choroidal hyperfluorescence with well-determined boundaries clearly discernible in the early phase of FA, with progressive leakage beyond the initial boundaries of the CNV and an area of early hypercyanescence without marked leakage activity on ICGA.

Patients with neovascular maculopathy from pathologic myopia, angioid streaks, infectious inflammatory chorioretinal disease, tumors, hereditary disorders or, or trauma were excluded.

The greatest horizontal dimension of the retinal leakage area according to ICGA was 1420 +/-670 um and according to SD OCT was 3473 +/-885 um (p=0.000, Pearson coefficient 0.65). The authors conclude that ICGA and FA seem to underestimate the extension of the neovascular complex and the associated retinal pathological features compared with SD OCT imaging.

- Study quality: Poor
- Applicability: Good

According to European Society of Retina Specialists (EURETINA) guideline [R4] fluorescein angiography (FA) is the only diagnostic examination that can confirm the mere existence of a CNV and if not contraindicated for systemic risks is routinely mandatory. Indocyanine green angiography (ICGA), when coupled with FA, can further reveal the area of focal hyperfluorescence or polypoidal choroidal vasculopathy.

- Study quality: Moderate
- Applicability: Good

References

R1=Mowatt G, Hernández R, Castillo M ym. Optical coherence tomography for the diagnosis, monitoring and guiding of treatment for neovascular age-related macular degeneration: a systematic review and economic evaluation. Health Technol Assess 2014;18:1-254 [PubMed](#)

R2=Landa G, Springer A, Bukelman A ym. The diagnostic contribution of indocyanine green to fluorescein angiography in fellow drusen eyes of patients with wet age-related macular degeneration. *Eur J Ophthalmol* 2007;17:615-9 [PubMed](#)

R3=Sulzbacher F, Kiss C, Munk M ym. Diagnostic evaluation of type 2 (classic) choroidal neovascularization: optical coherence tomography, indocyanine green angiography, and fluorescein angiography. *Am J Ophthalmol* 2011;152:799-806.e1 [PubMed](#)

R4=Schmidt-Erfurth U, Chong V, Loewenstein A ym. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *Br J Ophthalmol* 2014;98:1144-67 [PubMed](#)

nak08688

Interobserver interpretation of FA images in the diagnosis of wAMD

30.3.2016

Tanja Laukkala

Level of evidence = C**Interobserver interpretation of FA images in the diagnosis of wAMD may be variable.**

The aim of this retrospective study [R1] was to determine the rate of agreement among five retina specialists in classifying various angiographic features of subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD), as evaluated on printed digital fluorescein angiogram (FA) frames, as well as determination of eligibility for photodynamic treatment (PDT) according to established guidelines. Ninety-two digital FAs of 77 patients (27 men, 50 women) demonstrating subfoveal CNV secondary to AMD were obtained from the charts of patients attending to the Retina Unit of Tel Aviv Sourasky Medical Center (Tel Aviv, Israel), the patients were previously diagnosed as having CNV secondary to AMD and were evaluated independently by five retina specialists. The pattern of classic component could be classified as no classic component, minimally classic, predominantly classic, or classic only. Each grader was asked to determine eligibility of each case to PDT according to established treatment guidelines, national health insurance guidelines, and one's own personal judgment. The kappa coefficient of concordance calculated for all five observers regarding CNV localization was 0.285, indicating fair overall agreement, and was 0.295, indicating fair agreement, regarding classification of leakage pattern. The kappa coefficient of agreement calculated for all five graders regarding eligibility for treatment according to established international guidelines, national health insurance, and each grader's own personal judgment was 0.163, 0.33, and 0.164, respectively, indicating slight to fair overall agreement. The authors concluded that considerable variability may exist among retina specialists interpreting FAs and should be considered in the assessment of treatment guidelines.

- Study quality: Poor
- Applicability: Good

The aim of the study [R2] was to determine inter- and intraobserver agreement among Canadian retina specialists in their angiographic classification of choroidal neovascularization and their decision to treat with photodynamic therapy. Agreement was also determined between retina specialists and a Reading Center. All retina specialists in Canada were asked to participate in a

web-based survey, which consisted of 24 randomly selected cases of exudative AMD provided by the University of Wisconsin Fundus Photograph Reading Center. Forty retina specialists graded 24 cases of exudative age-related macular degeneration on two occasions separated by 6 months. Participants were asked to categorize the choroidal neovascularization and indicate if they would treat with photodynamic therapy. Agreement was determined for decision to treat and for interpretation of the fluorescein angiogram. Angiographic interpretation by participants was compared with that of the Reading Center.

The 40 retina specialists have been in practice for an average of 11.9 years with a SD of 9.1 year and have been treating patients with PDT for an average of 3.6 years (SD 1.9). They consisted of 27 surgical retina specialists, 9 medical retina specialists, and 4 retina fellows. The 24 cases selected by the reading center consisted of 9 predominantly classical lesions (PC), 5 minimally classic (MC), 6 occult with no classic (ONC) and 4 others (O). The response rate for treatment decision was 915/960 (95.3%) and 951/960 for lesion categorization (99.1%).

The kappas among the 40 participants for lesion categorization and treatment decision were 0.43 (95% confidence interval: 0.36-0.52) and 0.29 (95% confidence interval: 0.18-0.42), respectively. The kappa for intraobserver agreement was 0.57 (95% confidence interval: 0.50-0.64) for lesion categorization and 0.58 (95% confidence interval: 0.43-0.74) for treatment decision. The mean percent agreement with the Reading Center for lesion categorization was 65.4%. The authors concluded that there was moderate interobserver agreement for choroidal neovascularization categorization and poor agreement among Canadian retina specialists for decision to treat with photodynamic therapy. There was moderate intraobserver agreement for both treatment decision and lesion categorization. There was moderate agreement between observers and the Reading Center for angiographic choroidal neovascularization categorization.

- Study quality: Poor
- Applicability: Good

The aim of the study [R3] was to determine intraobserver and interobserver variation for classifying types of choroidal neovascularizations (CNV) in exudative age-related macular degeneration (ARMD). Digital high-quality fluorescein angiograms of 40 patients with neovascular ARMD were evaluated independently by 16 retinal specialists who were members of the European Fluorescein Angiography Club during a meeting in France in December 2000.

Fluorescein angiographies were presented in two randomized sequences (series A and B) to each masked reader for classification of type of CNV into classic, occult, or mixed with classic

component of less or greater 50%. Agreement was evaluated by calculating kappa statistics (kappa) and intraclass correlation coefficients.

The mean kappa coefficient was 0.64 +/- 0.11 for intraobserver variation, with a range from 0.44 to 0.89. For interobserver variation the intraclass correlation coefficients was calculated as 0.66 (95% confidence interval [CI] 0.56, 0.77) for series A and as 0.55 (95% CI 0.43, 0.67) for series B.

The authors conclude that angiographic classification of CNV secondary to ARMD can vary considerably not only between observers but also for repeated evaluation by the same observer. Because various current and emerging treatments including photodynamic therapy are based on specific angiographic characteristics, accurate interpretation was emphasized.

- Study quality: Poor
- Applicability: Good

To determine interobserver agreement for classifying choroidal neovascular membranes in age-related macular degeneration [R4] Six fluorescein angiograms of choroidal neovascular membranes were interpreted by 21 retina specialists who had been in practice for an average of 8.25 years (median 7 years, range 1.5–20 years) and were ophthalmologists with fellowship training in retinal disease. Reliability was measured by percent agreement and kappa coefficient. Interobserver agreement of membrane types ranged from perfect concordance for a small, classic membrane to near-random classification for a complex pattern. Mean kappa coefficient was .64. Interobserver agreement of membrane size was most variable for intermediate size lesions (mean kappa coefficient = 0.40). The authors concluded that fluorescein angiographic interpretation of choroidal neovascular membrane type and size can vary considerably. Interobserver agreement was better for membrane type than for membrane size.

- Study quality: Moderate
- Applicability: Moderate

References

R1=Zayit-Soudry S, Alfasi M, Goldstein M ym. Variability among retina specialists in evaluating fluorescein angiograms of patients with neovascular age-related macular degeneration. *Retina* 2007;27:798-803 [PubMed](#)

R2=Muni RH, Altaweel M, Tennant M ym. Agreement among Canadian retina specialists in the determination of treatment eligibility for photodynamic therapy in age-related macular degeneration. *Retina* 2008;28:1421-6 [PubMed](#)

R3=Holz FG, Jorzik J, Schutt F ym. Agreement among ophthalmologists in evaluating fluorescein angiograms in patients with neovascular age-related macular degeneration for photodynamic therapy eligibility (FLAP-study). *Ophthalmology* 2003;110:400-5 [PubMed](#)

R4=Friedman SM, Margo CE. Choroidal neovascular membranes: reproducibility of angiographic interpretation. *Am J Ophthalmol* 2000;130:839-41 [PubMed](#)

nak08689

Bevacizumab loading dose in the treatment of wAMD

30.3.2016

Jorma Komulainen

Level of evidence = C**Loading dose injections of bevacizumab given 3 times 4–6 weeks apart may lead to better improvement of visual acuity in the short term than a PRN protocol to begin with.**

In a randomized controlled study by Arias et al. [R1] 50 patients with choroidal neovascularization secondary to age-related macular degeneration were randomized to either bevacizumab administered once a month for 3 months and thereafter as needed (loading dose, LD) or bevacizumab administered as needed, after the first infection (pro re nata, PRN). During 6 months follow-up, mean visual acuity improved by 13.7 letters ($p < 0.001$) in the LD group and by 4.6 letters in the PRN group ($p < 0.001$). 36% of patients in the LD group compared with 12% in the PRN group gained 15 or more letters ($p = 0.04$). Mean foveal thickness decreased by 91.3 micrometers ($p < 0.001$) in the LD group and 48.2 micrometers in the PRN group ($p < 0.001$).

- Study quality: Moderate
- Applicability: Good

Comment: Small sample size and short follow-up.

In a randomized controlled study by Barikian et al. [R2] 90 patients with treatment-naïve age-related macular degeneration were randomized in three groups: (1) intravitreal bevacizumab every 2 weeks for 3 consecutive injections, (2) intravitreal bevacizumab every 4 weeks for 3 consecutive injections and (3) intravitreal bevacizumab immediate pro re nata after first injection. After the initial phase, patients were treated pro re nata and followed for 12 months. Mean initial fluid-free interval was 2.4, 3.4, and 3.5 months for biweekly induction, monthly induction, and immediate prn groups, respectively ($p = 0.03$). Significance was lost when corrected for age and sex ($p = 0.073$). Mean improvement in BCVA, central retinal thickness, and total number of injections were similar among the groups at 12 months. Six eyes in the biweekly induction group developed subretinal fibrosis vs no eyes in the other 2 groups ($p = 0.003$).

- Study quality: Moderate

- Applicability: Good

Comment: Sample size may have been too small to find clinically important differences between groups.

A total of 100 treatment-naive patients with active subfoveal choroidal neovascularisation of minimally classic or occult type, secondary to age-related macular degeneration, were randomized to receive either one injection of bevacizumab at baseline followed by a PRN regimen (NLD) or three 6-weekly injections of bevacizumab followed by PRN (LD) [R3]. Primary end point was best corrected visual acuity. Secondary end points were central macular thickness (CMT) on OCT and adverse events. Proportions of patients with visual stability, defined as 15 or less letter loss from baseline, were 84% in the LD group compared with only 67% in the NLD group ($p < 0.05$). A post hoc analysis comparing the two groups in terms of the mean visual scores turned out to be not statistically significant. There were no between-groups differences in CMT. There were no serious ocular adverse events in either group. In total, there were six treatment-emergent adverse events in the LD group and five in the NLD group.

- Study quality: Moderate
- Applicability: Good

References

R1=Arias L, Caminal JM, Casas L ym. A study comparing two protocols of treatment with intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Br J Ophthalmol 2008;92:1636-41 [PubMed](#)

R2=Barikian A, Mahfoud Z, Abdulaal M ym. Induction with intravitreal bevacizumab every two weeks in the management of neovascular age-related macular degeneration. Am J Ophthalmol 2015;159:131-7 [PubMed](#)

R3=Menon G, Chandran M, Sivaprasad S ym. Is it necessary to use three mandatory loading doses when commencing therapy for neovascular age-related macular degeneration using bevacizumab? (BeMOc Trial). Eye (Lond) 2013;27:959-63 [PubMed](#)

nak08690

Anti-VEGF protocols in the treatment of wet AMD: efficacy

30.3.2016

Jorma Komulainen

Level of evidence = C**During short-term follow-up, bevacizumab and ranibizumab injected at fixed 4-6-week intervals may not lead to better visual acuity than drugs injected according to PRN protocol.**

In the meta-analysis [R1] ranibizumab and bevacizumab treatment regimens (monthly or as-needed/quarterly) were compared. Altogether 8 studies fulfilled the criteria and were included in the analysis. The dependent variable was visual acuity outcome, which was defined as either the effect size of letters gained (continuous) or whether or not a patient gained ≥ 15 letters in visual acuity (dichotomous). Minimum follow-up period was 12 months. The weighted regression on the 13 sets of comparisons revealed that patients with monthly treatment regimens had higher visual acuity gains compared with patients in the as needed/quarterly treatment group. ($\beta = 0.441$, $P < 0.05$). Also, more patients on the monthly treatment regimen gained ≥ 15 letters than patients treated on the as-needed/quarterly regimen ($\beta = 0.582$, $P < 0.05$).

- Study quality: High
- Applicability: Good

Comment: There was a great heterogeneity between the studies. IVAN and HARBOR studies were not included in analysis.

In the HARBOR study [R2] 1098 patients with subfoveal wet age-related macular degeneration (AMD) were randomized to get ranibizumab 0.5 mg or 2.0 mg intravitreal injections administered monthly or on a pro re nata (PRN) basis after 3 monthly loading doses for 12 months. Primary end point was mean change from baseline in best corrected visual acuity (BCVA) at month 12. Secondary end points were mean number of ranibizumab injections, mean change from baseline in central foveal thickness (CFT) over time and proportion of patients who gained at least 15 letters of BCVA. Neither statistically significant difference between the four groups were demonstrated in primary nor in secondary end points.

- Study quality: High

- Applicability: Good

The 24 months follow-up results from the HARBOR study [R3] showed no statistically significant differences between the above-mentioned groups. The proportion of patients who gained 15 letters in BCVA from baseline (i.e., 3-line gainers using the ETDRS chart) at month 24 was 34.5%, 33.1%, 37.6%, and 34.5% in the 0.5 mg monthly, 0.5 mg PRN, 2.0 mg monthly, and 2.0 mg PRN groups, respectively. During year 1, the ranibizumab monthly dosed groups averaged 11.3 (0.5 mg) and 11.2 (2.0 mg) injections, whereas the ranibizumab PRN-dosed groups averaged 7.7 (0.5 mg) and 6.9 (2.0 mg) injections. During year 2, the ranibizumab monthly dosed groups averaged 10.1 (0.5 mg) and 10.4 (2.0 mg) injections, and the ranibizumab PRN-dosed groups averaged 5.6 (0.5 mg) and 4.3 (2.0 mg) injections.

- Study quality: High
- Applicability: Good

In the CATT study [R4], 1185 patients with neovascular AMD were initially enrolled in the clinical trial, whereas 1107 of them were followed-up for 2 years. Patients were randomized in 4 groups: ranibizumab 0.5 mg or bevacizumab 1.25 mg and dosing regimen monthly or as needed. At 1 year, patients initially assigned to monthly treatment were reassigned randomly to monthly or as-needed treatment, without changing the drug assignment. Primary end point was mean change in visual acuity. Secondary end points were: proportion of patients with a change in visual acuity of ≥ 15 letters, number of injections, drug costs, presence of fluid and change in foveal retinal thickness, change in lesion size on fluorescein angiography and incidence of systemic and ocular adverse events.

Mean gain was greater for monthly than for as-needed treatment (difference, -2.4 letters; 95% CI, -4.8 to -0.1; $p=0.046$). After adjusting for baseline predictors of visual acuity in a multivariable longitudinal regression model, the estimated change in visual acuity, averaged over 2 years of follow-up, was 1.7 letters better for patients treated monthly (CI: [-0.1, 3.4]; $p=0.07$).

The mean (standard deviation) number of injections through year 2 in the as-needed groups, out of a maximum of 26, was 12.6 (6.6) for patients treated with ranibizumab and 14.1 (7.0) for those treated with bevacizumab ($p=0.01$). The estimated 2-year drug cost per patient varied from \$705 in the bevacizumab-as-needed group to \$44,800 in the ranibizumab-monthly group. At 2 years, mean retinal thickness was 29 μm less in patients treated monthly than in patients treated with an as-needed regimen (regimen $p=0.005$).

The proportion of patients without fluid on OCT ranged from 13.9% in the bevacizumab-as-needed group to 45.5% in the ranibizumab-monthly group (drug $p=0.0003$; regimen $p<0.0001$). Fluorescein

dye leakage was absent in a higher percentage of patients treated monthly than in patients treated as needed (regimen $p=0.002$).

The proportion of patients with 1 or more systemic serious adverse events was higher with bevacizumab than ranibizumab (39.9% vs. 31.7%; adjusted risk ratio, 1.30; 95% CI, 1.07-1.57; $p=0.009$). Patients treated as needed had higher rates than patients treated monthly (risk ratio 1.20; CI: [0.98, 1.47]; $p=0.08$).

- Study quality: High
- Applicability: Good

One hundred twenty eyes of 120 patients with treatment-naïve subfoveal neovascular AMD were randomized to receive either fixed-interval dosing (every 4 to 6 weeks) or variable dosing with intravitreal bevacizumab 1.25 mg for 12 months [R5]. Primary end point was best-corrected visual acuity. Secondary end point was central retinal thickness. No differences between groups were found.

- Study quality: Moderate
- Applicability: Good

A total of 191 patients with exudative AMD were randomized to receive 1-year continuous regimen of intravitreal bevacizumab every 4, 6 or 8 weeks [R6]. Primary end point was visual acuity change after 1 year of treatment. Secondary end points were change in fluid and foveal thickness and proportion of patients with a change in visual acuity of 15 letters or more. There was no statistically significant difference in the mean change of visual acuity score at 1 year for bevacizumab administered every 4 (1.96 +/- 13.70), 6 (1.60 +/- 10.98) or 8 weeks (5.98 +/- 8.88), nor were there any differences in secondary end points.

- Study quality: Moderate
- Applicability: Good

A total of 353 patients with primary or recurrent subfoveal CNV secondary to AMD were randomized to receive 0.3 mg quarterly, 0.5 mg quarterly, or 0.3 mg monthly doses of ranibizumab. Treatment comprised of a loading phase (3 consecutive monthly injections) followed by a 9-month maintenance phase (either monthly or quarterly injection) [R7]. Primary end point was mean change in best-corrected visual acuity (BCVA). Secondary end points were central retinal thickness (CRT) and incidence of adverse events (AEs). In the per-protocol population (293 patients), BCVA, measured by Early Treatment Diabetic Retinopathy Study-like charts, increased from baseline to

month 12 by 4.9, 3.8, and 8.3 letters in the 0.3 mg quarterly (104 patients), 0.5 mg quarterly (88 patients), and 0.3 mg monthly (101 patients) dosing groups, respectively. Similar results were observed in the intent-to-treat (ITT) population (353 patients). Thus, the non-inferiority of a quarterly regimen was not achieved with reference to 5.0 letters. The mean decrease in CRT from baseline to month 12 in the ITT population was -96.0 letters in 0.5 mg quarterly, -105.6 letters in 0.3 mg quarterly, and -105.3 letters in 0.3 mg monthly. The mean decrease in CRT from baseline to month 12 in the ITT population was -96.0 letters in 0.5 mg quarterly, -105.6 letters in 0.3 mg quarterly, and -105.3 letters in 0.3 mg monthly. conjunctival hemorrhage (17.6%, pooled quarterly groups; 10.4%, monthly group) and eye pain (15.1%, pooled quarterly groups; 20.9%, monthly group).

- Study quality: Moderate
- Applicability: Good

References

R1=Jiang S, Park C, Barner JC. Ranibizumab for age-related macular degeneration: a meta-analysis of dose effects and comparison with no anti-VEGF treatment and bevacizumab. *J Clin Pharm Ther* 2014;39:234-9 [PubMed](#)

R2=Busbee BG, Ho AC, Brown DM ym. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology* 2013;120:1046-56 [PubMed](#)

R3=Ho AC, Busbee BG, Regillo CD ym. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology* 2014;121:2181-92 [PubMed](#)

R4=Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG ym. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;119:1388-98 [PubMed](#)

R5=El-Mollayess GM, Mahfoud Z, Schakal AR ym. Fixed-interval versus OCT-guided variable dosing of intravitreal bevacizumab in the management of neovascular age-related macular degeneration: a 12-month randomized prospective study. *Am J Ophthalmol* 2012;153:481-489.e1 [PubMed](#)

R6=Lushchik T, Amarakoon S, Martinez-Ciriano JP ym. Bevacizumab in age-related macular degeneration: a randomized controlled trial on the effect of injections every 4 weeks, 6 weeks and 8 weeks. *Acta Ophthalmol* 2013;91:e456-61 [PubMed](#)

R7=Schmidt-Erfurth U, Eldem B, Guymer R ym. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. Ophthalmology 2011;118:831-9 [PubMed](#)

nak08691

Anti-VEGF protocols in treatment of wet AMD: risk of harms

30.3.2016

Jorma Komulainen

Level of evidence = C

Monthly injections of bevacizumab or ranibizumab may increase risk for geographic retinal atrophy compared to PRN protocol. Otherwise no clinically significant difference seem to appear in the risk of adverse effects between the treatment protocols.

A meta-analysis of randomized trials of ranibizumab for age-related macular degeneration (AMD) to elucidate systemic vascular risk included 11 trials comprising 6596 patients with AMD [R1]. Comparisons between different intensities of ranibizumab regimens in terms of dose and retreatment frequency were performed. End points were incidence of cerebrovascular accidents (CVAs), myocardial infarctions, non-ocular hemorrhages, overall arterial thromboembolic events (ATEs), and all-cause mortality. A non-significant increase was observed in monthly vs. pro re nata risk for CVA (OR, 2.04; 95%CI, 0.94-4.45; p=0.07), non-ocular hemorrhages (OR, 1.54; 95% CI, 0.98-2.42; p=0.06) and ATEs (OR, 1.58; 95% CI, 0.96-2.61; p=0.07).

- Study quality: High
- Applicability: Good

Comment: A significant increase in the risk for CVA was demonstrated, when monthly dosing was compared with combined 0 mg/PRN group (OR, 1.89; 95% CI, 1.06-3.38; p=0.03).

In the CATT study [R2] 1185 patients with neovascular AMD were initially enrolled in the clinical trial, whereas 1107 of them were followed-up for 2 years. Patients were randomized in 4 groups: ranibizumab 0.5 mg or bevacizumab 1.25 mg and dosing regimen monthly or as needed. At 1 year, patients initially assigned to monthly treatment were reassigned randomly to monthly or as-needed treatment, without changing the drug assignment. Primary end point was mean change in visual acuity. Secondary end points were: proportion of patients with a change in visual acuity of ≥ 15 letters, number of injections, drug costs, presence of fluid and change in foveal retinal thickness, change in lesion size on fluorescein angiography and incidence of systemic and ocular adverse events.

Mean gain was greater for monthly than for as-needed treatment (difference, -2.4 letters; 95% CI, -4.8 to -0.1; $p=0.046$). After adjusting for baseline predictors of visual acuity in a multivariable longitudinal regression model, the estimated change in visual acuity, averaged over 2 years of follow-up, was 1.7 letters better for patients treated monthly (CI: [-0.1, 3.4]; $p=0.07$).

The mean (standard deviation) number of injections through year 2 in the as-needed groups, out of a maximum of 26, was 12.6 (6.6) for patients treated with ranibizumab and 14.1 (7.0) for those treated with bevacizumab ($p=0.01$). The estimated 2-year drug cost per patient varied from \$705 in the bevacizumab-as-needed group to \$44,800 in the ranibizumab-monthly group. At 2 years, mean retinal thickness was 29 μm less in patients treated monthly than in patients treated with an as-needed regimen (regimen $p=0.005$).

The proportion of patients without fluid on OCT ranged from 13.9% in the bevacizumab-as-needed group to 45.5% in the ranibizumab-monthly group (drug $p=0.0003$; regimen $p<0.0001$). Fluorescein dye leakage was absent in a higher percentage of patients treated monthly than in patients treated as needed (regimen $p=0.002$).

The proportion of patients with 1 or more systemic serious adverse events was higher with bevacizumab than ranibizumab (39.9% vs. 31.7%; adjusted risk ratio, 1.30; 95% CI, 1.07-1.57; $p=0.009$). Patients treated as needed had higher rates than patients treated monthly, but the difference was not statistically significant (risk ratio 1.20; CI: [0.98, 1.47]; $p=0.08$).

- Study quality: High
- Applicability: Good

In the IVAN trial [R3] 610 patients with untreated neovascular AMD were randomized in 4 groups: 0.5 mg ranibizumab given continuously (monthly) for 2 years; 0.5 mg ranibizumab given continuously (monthly) for 3 months, followed by further courses on 3 monthly injections if clinically indicated; 1.25 mg bevacizumab given continuously (monthly) for 2 years; 1.25 mg bevacizumab given continuously (monthly) for 3 months, followed by further courses on 3 monthly injections if clinically indicated. The primary end points were quality-adjusted life-years (QALYs) and their costs (costs incurred by patients and their families or employers were excluded).

The number of QALYs accrued over the 2-year trial period did not differ significantly between bevacizumab and ranibizumab, or between continuous and discontinuous treatments ($p\geq 0.381$). Ranibizumab was significantly more costly than bevacizumab for both continuous (+£14,989/patient [\$23,468]; 95% CI £14,522 to £15,456; $p<0.001$). Using continuous rather than discontinuous treatment increased costs by £7,090 (\$11,102 (95% CI £6,337 to £7,844), $p<0.001$) for ranibizumab and £599 (\$938 [95% CI £91 to £1,107], $p=0.021$) for bevacizumab. The cost of

medication changes, hospitalisations and ambulatory consultations associated with expected SAEs and expected AEs was relatively small (mean: £469 [\$735] per patient), but varied substantially between patients (95th centile range: £0, £1401). There was no significant difference in such costs between drugs or between treatment regimens ($p \geq 0.163$).

- Study quality: High
- Applicability: Moderate

Comment: Exclusion of costs incurred by patients, families and employers may underestimate the difference between continuous and discontinuous regimens.

In a cohort within a randomized clinical trial, the risk of development of geographical atrophy (GA) in patients with AMD was studied [R4]. Patients were those 1024 CATT patients with AMD and with no GA visible on color fundus photographs (CFPs) and/or fluorescein angiograms (FAs) at enrollment. The randomized treatment groups were ranibizumab monthly, ranibizumab pro re nata, bevacizumab monthly and bevacizumab pro re nata. During the 2 years follow-up, GA developed in 187 of 1024 patients (18.3%). Ranibizumab compared with bevacizumab had a higher risk (aHR, 1.43; 95% CI, 1.06–1.93), and monthly dosing had a higher risk (aHR, 1.59; 95% CI, 1.17–2.16) than PRN dosing.

- Study quality: Moderate
- Applicability: Good

A total of 353 patients with primary or recurrent subfoveal CNV secondary to AMD were randomized to receive 0.3 mg quarterly, 0.5 mg quarterly, or 0.3 mg monthly doses of ranibizumab. Treatment comprised of a loading phase (3 consecutive monthly injections) followed by a 9-month maintenance phase (either monthly or quarterly injection) [R5]. Primary end point was mean change in best-corrected visual acuity (BCVA). Secondary end points were central retinal thickness (CRT) and incidence of adverse events (AEs). In the per-protocol population (293 patients), BCVA, measured by Early Treatment Diabetic Retinopathy Study-like charts, increased from baseline to month 12 by 4.9, 3.8, and 8.3 letters in the 0.3 mg quarterly (104 patients), 0.5 mg quarterly (88 patients), and 0.3 mg monthly (101 patients) dosing groups, respectively. Similar results were observed in the intent-to-treat (ITT) population (353 patients). Thus, the noninferiority of a quarterly regimen was not achieved with reference to 5.0 letters. The mean decrease in CRT from baseline to month 12 in the ITT population was -96.0 μm in 0.3 mg quarterly, -105.6 μm in 0.5 mg quarterly, and -105.3 μm in 0.3 mg monthly group. The most frequent ocular AEs were conjunctival hemorrhage (17.6%, pooled quarterly groups; 10.4%, monthly group) and eye pain (15.1%, pooled quarterly groups; 20.9%, monthly group).

- Study quality: Moderate
- Applicability: Good

A prospective cohort study within a randomized clinical trial assessed risk factors for scar in eyes treated with ranibizumab or bevacizumab for neovascular AMD [R6]. Included were patients with no scar on color fundus photography (CFP) or fluorescein angiography (FA) at enrollment in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT). Eyes were assigned to ranibizumab or bevacizumab treatment and to 1 of 3 dosing regimens for 2 years. Scar developed in 480 of 1059 eyes (45.3%) by 2 years. Drug and dosing regimen had no statistically significant association with scarring.

- Study quality: Moderate
- Applicability: Good

The purpose of the study [R7] was to determine efficacy and safety of intravitreal aflibercept in patients with AMD during a second year of variable dosing after a first-year fixed-dosing period. At baseline 2457 patients were randomised to receive 0.5 mg intravitreal ranibizumab every 4 weeks (Rq4), 2 mg aflibercept every 4 weeks (2q4), 0.5 mg aflibercept every 4 weeks (0.5q4), or 2 mg aflibercept every 8 weeks (2q8) after 3 monthly injections. A total of 2235 patients entered the follow-up study and 2063 (91.0%) completed it. During weeks 52 through 96, patients received their original dosing assignment using an as-needed regimen with defined retreatment criteria and mandatory dosing at least every 12 weeks. There were no significant drug or dosing regimen associated differences in adverse events. Most common ocular adverse events were conjunctival hemorrhage (range 23.7-29.9%), retinal hemorrhage (13.6-16.2%), reduced visual acuity (11.3-13.0%), eye pain (8.9-12.1%), vitreous detachment (7.7-10.0%), and increased intraocular pressure (6.2-10.8%) from baseline to week 96. Intraocular inflammation was reported for 1.5%, 1.1%, 0.8%, and 0.5% for Rq4, 2q4, 0.5q4 and 2q8 groups. Serious ocular adverse events occurred for 4.4%, 3.6%, 3.2%, and 3.9%, respectively. The figures for serious non-ocular adverse events were 24.5%, 21.4%, 25.3%, and 25.2%. These events included atrial fibrillation, myocardial infarction, pneumonia, fall, congestive heart failure, coronary artery disease, TIA, cerebrovascular accident, COPD and osteoarthritis. Percentage of specific arterial thromboembolic end points as set forth by the Anti-Platelet Trialists' Collaboration was 3.2% for Rq4 group and 2.4% for 2q4, 3.8% for 0.5q4, and 3.6% for 2q8. The percentage of nonfatal myocardial infarction ranged from 1.0 to 2.0% and nonfatal stroke from 0.5% to 0.8%. The percentage of deaths was 2.7%, 2.1%, 3.2%, and 3.3% for the groups.

- Study quality: Moderate

- Applicability: Good

References

R1=Ueta T, Noda Y, Toyama T ym. Systemic vascular safety of ranibizumab for age-related macular degeneration: systematic review and meta-analysis of randomized trials. *Ophthalmology* 2014;121:2193-203.e1-7 [PubMed](#)

R2=Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG ym. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;119:1388-98 [PubMed](#)

R3=Dakin HA, Wordsworth S, Rogers CA ym. Cost-effectiveness of ranibizumab and bevacizumab for age-related macular degeneration: 2-year findings from the IVAN randomised trial. *BMJ Open* 2014;4:e005094 [PubMed](#)

R4=Grunwald JE, Daniel E, Huang J ym. Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials. *Ophthalmology* 2014;121:150-61 [PubMed](#)

R5=Schmidt-Erfurth U, Eldem B, Guymer R ym. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. *Ophthalmology* 2011;118:831-9 [PubMed](#)

R6=Daniel E, Toth CA, Grunwald JE ym. Risk of scar in the comparison of age-related macular degeneration treatments trials. *Ophthalmology* 2014;121:656-66 [PubMed](#)

R7=Schmidt-Erfurth U, Kaiser PK, Korobelnik JF ym. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology* 2014;121:193-201 [PubMed](#)

nak08692

Anti-VEGF protocols in treatment of wet AMD: costs

25.4.2016

Jorma Komulainen

Level of evidence = B

Bevacizumab injected for wAMD as needed seems to be a more cost-effective treatment protocol than monthly injections, in which small increases in effects incur higher additional costs. Bevacizumab seems to be more cost-effective than ranibizumab and aflibercept given as needed or monthly.

In the CATT study [R1]1185 patients with neovascular AMD were initially enrolled in the clinical trial, whereas 1107 of them were followed-up for 2 years. Patients were randomized in 4 groups: ranibizumab 0.5 mg or bevacizumab 1.25 mg and dosing regimen monthly or as needed. At 1 year, patients initially assigned to monthly treatment were reassigned randomly to monthly or as-needed treatment, without changing the drug assignment. Primary end point was mean change in visual acuity. Secondary end points were: proportion of patients with a change in visual acuity of ≥ 15 letters, number of injections, drug costs, presence of fluid and change in foveal retinal thickness, change in lesion size on fluorescein angiography and incidence of systemic and ocular adverse events.

Mean gain was greater for monthly than for as-needed treatment (difference, -2.4 letters; 95% CI, -4.8 to -0.1; $p=0.046$). After adjusting for baseline predictors of visual acuity in a multivariable longitudinal regression model, the estimated change in visual acuity, averaged over 2 years of follow-up, was 1.7 letters better for patients treated monthly (CI: [-0.1, 3.4]; $p=0.07$).

The mean (standard deviation) number of injections through year 2 in the as-needed groups, out of a maximum of 26, was 12.6 (6.6) for patients treated with ranibizumab and 14.1 (7.0) for those treated with bevacizumab ($p=0.01$). The estimated 2-year drug cost per patient varied from \$705 in the bevacizumab-as-needed group to \$44,800 in the ranibizumab-monthly group. At 2 years, mean retinal thickness was 29 μm less in patients treated monthly than in patients treated with an as-needed regimen (regimen $p=0.005$).

The proportion of patients without fluid on OCT ranged from 13.9% in the bevacizumab-as-needed group to 45.5% in the ranibizumab-monthly group (drug $p=0.0003$; regimen $p<0.0001$). Fluorescein

dye leakage was absent in a higher percentage of patients treated monthly than in patients treated as needed (regimen $p=0.002$).

The proportion of patients with 1 or more systemic serious adverse events was higher with bevacizumab than ranibizumab (39.9% vs. 31.7%; adjusted risk ratio, 1.30; 95% CI, 1.07-1.57; $p=0.009$). Patients treated as needed had higher rates than patients treated monthly (risk ratio 1.20; CI: [0.98, 1.47]; $p=0.08$).

- Study quality: High
- Applicability: Good

In the IVAN trial [R2] 610 patients with untreated neovascular AMD were randomized in 4 groups: 0.5 mg ranibizumab given continuously (monthly) for 2 years; 0.5 mg ranibizumab given continuously (monthly) for 3 months, followed by further courses on 3 monthly injections if clinically indicated; 1.25 mg bevacizumab given continuously (monthly) for 2 years; 1.25 mg bevacizumab given continuously (monthly) for 3 months, followed by further courses on 3 monthly injections if clinically indicated. The primary end points were quality-adjusted life-years (QALYs) assessed with EQ-5D questionnaire and their costs (costs incurred by patients and their families or employers were excluded).

The number of QALYs accrued over the 2-year trial period did not differ significantly between bevacizumab and ranibizumab, or between continuous and discontinuous treatments ($p\geq 0.381$). Ranibizumab was significantly more costly than bevacizumab for both continuous (+£14 989/patient [\$23 468]; 95%CI £14 522 to £15 456; $p<0.001$). Using continuous rather than discontinuous treatment increased costs by £7090 (\$11 102 (95% CI £6337 to £7844), $p<0.001$) for ranibizumab and £599 (\$938 [95% CI £91 to £1107], $p=0.021$) for bevacizumab. The cost of medication changes, hospitalisations and ambulatory consultations associated with expected SAEs and expected AEs was relatively small (mean: £469 [\$735] per patient), but varied substantially between patients (95th centile range: £0, £1401). There was no significant difference in such costs between drugs or between treatment regimens ($p\geq 0.163$).

- Study quality: High
- Applicability: Moderate

Comment: Exclusion of costs incurred by patients, families and employers may underestimate the difference between continuous and discontinuous regimens. ED-5Q questionnaire does not include parts specific to eye problems, and may thus not be sensitive enough for this purpose.

In a cost-utility study [R3] a patient-level, visual acuity-based, 2-eye model was developed to compare the cost-utility of aflibercept, ranibizumab and bevacizumab treatment in patients with wet AMD. Data on effectiveness were derived from randomized controlled trials evaluating the outcomes of aflibercept, bevacizumab, and ranibizumab. Utility and resource utilization were assessed in interviews with AMD patients. Costs were based on standard health care cost prices. Time horizons were two and five years. A societal perspective was employed.

Over five years, costs associated with aflibercept treatment were €36.030, with 2.15 QALYs. Costs associated with the bevacizumab regimens, ABC study as-needed (PRN); CATT study PRN; and CATT study 1x/month, were €19.367; €26.746; and €30.520, with 2.16; 2.17; and 2.15 QALYs, respectively. Costs associated with ranibizumab PRN and 1x/month were €45.491 and €74.837 with 2.16 and 2.15 QALYs, respectively. 'No treatment' was associated with €9530 and 1.96 QALYs. The incremental cost-effectiveness ratios versus 'no treatment' were: aflibercept- €140.274; bevacizumab- €51.062 (ABC PRN), €83.256 (CATT PRN) and €110.361 (1x/month); ranibizumab- €181.667 (PRN) and €349.773 (1x/month). Results were highly dependent on whether only one or both eyes were included, length of time horizon, and whether the costs of blindness and low-vision were included in the analysis.

- Study quality: Moderate
- Applicability: Poor

In a cost-utility study [R3] a patient-level, visual acuity-based, 2-eye model was developed to compare the cost-utility of aflibercept, ranibizumab and bevacizumab treatment in patients with wet AMD. Data on effectiveness were derived from randomized controlled trials evaluating the outcomes of aflibercept, bevacizumab, and ranibizumab. Utility and resource utilization were assessed in interviews with AMD patients. Costs were based on standard health care cost prices. Time horizons were two and five years. A societal perspective was employed.

Using a mathematical model with a 20-year time horizon, a study from the USA compared the incremental cost-effectiveness of treating a hypothetical cohort of 80-year-old patients with newly diagnosed neovascular macular degeneration using monthly bevacizumab, as-needed bevacizumab, monthly ranibizumab, or as-needed ranibizumab [B4]. Data came from the Comparison of Age-related macular degeneration Treatment Trial (CATT), the Medicare Fee Schedule, and the medical literature.

Compared with as-needed bevacizumab, the incremental cost-effectiveness ratio of monthly bevacizumab is \$242 357/QALY. Monthly ranibizumab gains an additional 0.02 QALYs versus monthly bevacizumab at an incremental cost-effectiveness ratio of more than \$10 million/QALY.

As-needed ranibizumab was dominated by monthly bevacizumab, meaning it was more costly and less effective. In sensitivity analyses assuming a willingness to pay of \$100 000/QALY, the annual risk of serious vascular events would have to be at least 2.5 times higher with bevacizumab than that observed in the CATT trial for as-needed ranibizumab to have an incremental cost-effectiveness ratio of <\$100 000/QALY.

- Study quality: Moderate
- Applicability: Poor

References

R1=Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG ym. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;119:1388-98 [PubMed](#)

R2=Dakin HA, Wordsworth S, Rogers CA ym. Cost-effectiveness of ranibizumab and bevacizumab for age-related macular degeneration: 2-year findings from the IVAN randomised trial. *BMJ Open* 2014;4:e005094 [PubMed](#)

R3=Elshout M, van der Reis MI, Webers CA ym. The cost-utility of aflibercept for the treatment of age-related macular degeneration compared to bevacizumab and ranibizumab and the influence of model parameters. *Graefes Arch Clin Exp Ophthalmol* 2014;252:1911-20 [PubMed](#)

R4=Stein JD, Newman-Casey PA, Mrinalini T ym. Cost-effectiveness of bevacizumab and ranibizumab for newly diagnosed neovascular macular degeneration. *Ophthalmology* 2014;121:936-45 [PubMed](#)

nak08693

Aflibercept in treatment-resistant wet AMD

30.3.2016

Jorma Komulainen

Level of evidence = D

Within about 1-year, aflibercept may improve visual acuity and decrease anatomical changes in patients for whom other anti-VEGF drugs have not produced expected effect. However, high quality evidence is missing.

In a prospective, open-label, non-controlled trial [R1] 49 patient with treatment-resistant neovascular age-related macular degeneration (AMD) were treated with 2 mg intravitreal aflibercept administered as 3 initial loading doses every 4 weeks, followed by further injections every 8 weeks across a 24-weeks period in total. Outcomes assessed included proportions of patients with a gain or loss of more than 5 ETDRS letters and a decrease or increase in central retinal thickness (CRT) of more than 150 μ m at week 24, change in mean best corrected visual acuity (BCVA) and CRT and descriptive safety data. The BCVA improved and CRT was reduced at all follow-up visits compared with baseline ($p < 0.001$), with a mean improvement of 6.9 letters of BCVA and a decrease of 89.4 micrometers in CRT at week 24. There was 1 patient (2%) who lost more than 5 ETDRS letters and 27 (55%) who improved by 5 letters or more. There were 4 serious ocular adverse events, 1 deep vein thrombosis and 1 myocardial infarction.

- Study quality: Poor
- Applicability: Good

Total of 26 patients with exudative AMD, previously treated with ranibizumab and/or bevacizumab, were enrolled in a 12-months treatment with 2 mg aflibercept every months for 3 months, followed by a fixed dosing schedule of 2 mg aflibercept every 2 months [R2]. The primary end point was the mean absolute change from baseline central subfield thickness (CST) at months 12. Secondary outcomes were change from baseline best-corrected visual acuity (BCVA) score, percentage of patients who gained or lost greater than or equal to 15 letters of vision, percentage of patients who are 20/40 or better, percentage of patients who are 20/200 or worse, and the incidence of adverse and serious adverse events. Planned 6-month interim analysis demonstrated a mean decrease in CST of 38.6

 μ m ($p < 0.00$

of patients experienced a greater than 15-letter improvement in BCVA, while no patient lost 3 lines on vision. Forty-two percent of subjects were 20/40 or better, and 11.5% of patients were 20/200 or worse at month 6. No serious ocular or systemic adverse events were encountered.

- Study quality: Poor
- Applicability: Good

A 12 months follow-up of the patients described above, showed a mean increase in ETDRS BCVA of 9.2 letters ($p < 0.001$) and a mean decrease in CST of 50.3 micrometers ($p < 0.001$) [R3]. Twenty-seven percent of subjects experienced a 15-letter or more improvement in visual acuity, and no subject lost 3 lines or more of vision from baseline.

- Study quality: Poor
- Applicability: Good

A retrospective survey of 221 patients with wet AMD [R4], who were converted from ranibizumab or bevacizumab to aflibercept (adjusted every 7 weeks without a loading dose), showed no significant improvement in visual acuity or retinal thickness during the first 3 follow-up visits.

- Study quality: Poor
- Applicability: Good

Comment: None of these studies report the development of the vision before enrollment in the study.

References

R1=Chang AA, Li H, Broadhead GK ym. Intravitreal aflibercept for treatment-resistant neovascular age-related macular degeneration. *Ophthalmology* 2014;121:188-92 [PubMed](#)

R2=Singh RP, Srivastava S, Ehlers JP ym. A single-arm, investigator-initiated study of the efficacy, safety and tolerability of intravitreal aflibercept injection in subjects with exudative age-related macular degeneration, previously treated with ranibizumab or bevacizumab: 6-month interim analysis. *Br J Ophthalmol* 2014;98(Suppl 1):i22-27 [PubMed](#)

R3=Singh RP, Srivastava SK, Ehlers JP ym. A single-arm, investigator-initiated study of the efficacy, safety, and tolerability of intravitreal aflibercept injection in subjects with exudative age-related macular degeneration previously treated with ranibizumab or bevacizumab (ASSESS study): 12-month analysis. *Clin Ophthalmol* 2015;9:1759-66 [PubMed](#)

R4=Ferrone PJ, Anwar F, Naysan J ym. Early initial clinical experience with intravitreal aflibercept for wet age-related macular degeneration. Br J Ophthalmol 2014;98(Suppl 1):i17-21 [PubMed](#)

nak08694

Initiating anti-VEGF treatment immediately after diagnosis of wet AMD

30.3.2016

Jorma Komulainen

Level of evidence = C**Initiating anti-VEGF treatment within a few days after the diagnosis than after about 2-week delay may lead to better improvement of vision during 3-month follow-up.**

A retrospective survey [R1] was conducted in Denmark, in order to study the relation between the interval from diagnosis to initiation of intravitreal anti-VEGF injection therapy and visual outcome in neovascular age-related macular degeneration (nAMD). The study included 1185 eyes in 1099 patients who began ranibizumab treatment for nAMD during four separate periods in 2007, 2009, 2011 and 2012. The best-corrected visual acuity (BCVA) at the diagnosis remained within the range 0.23-0.24 Snellen and the median patient age within 79-80 years. The median time from diagnosis to treatment was 16 days in 2007, 11 days in 2009, 2 days in 2011 and 1 day in 2012. Simultaneously, BCVA at first visit after the third monthly injection increased from 0.24 to 0.31 Snellen ($p < 0.0001$) in concert with a shift in preferred practice from separate-day injection to same-day injection. Also the mean number of letters gained increased (2.6 in 2007, 0.4 in 2009, 5.3 in 2011 and 6.3 in 2012).

- Study quality: Moderate
- Applicability: Good

References

R1=Rasmussen A, Brandt S, Fuchs J ym. Visual outcomes in relation to time to treatment in neovascular age-related macular degeneration. Acta Ophthalmol 2015;93:616-20 [PubMed](#)

nak08695

Aflibercept and ranibizumab in treatment of wet AMD: quality of life

30.3.2016

Jorma Komulainen

Level of evidence = B**Ranibizumab monthly and aflibercept bimonthly both seem to improve the quality of life of patients and show no differences in this respect.**

Altogether 2419 patients with wet AMD, included in VIEW 1 and 2 studies, were randomized (after initial 3 monthly doses) to receive intravitreal aflibercept 2.0 mg every 8 weeks (2q8), aflibercept 2.0 mg every 4 weeks, aflibercept 0.5 mg every 4 weeks or ranibizumab 0.5 mg every 4 weeks (0.5q4) [R1]. The 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) was administered at baseline and at weeks 12, 24, 36 and 52. The NEI VFC-21 subscales were compared between aflibercept 2q8 and ranibizumab 0.5q4 groups. There were no differences in NEI VFQ-25 scores at the baseline. Also mean increase from baseline to 52 weeks was similar for aflibercept 2q8 and ranibizumab 0.5q4 groups (7.3 and 7.8 points, respectively), with clinically meaningful improvement recorded in 6 of 12 subscales (general vision, near activities, distance activities, mental health, role difficulties and dependency). Improvement in NEI VFQ-25 scores was seen in only those patients who gained more than 5 EDTRS letters.

- Study quality: High
- Applicability: Good

References

R1=Yuzawa M, Fujita K, Wittrup-Jensen KU ym. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. *Ophthalmology* 2015;122:571-8 [PubMed](#)

nak08696

Ranibizumab and bevacizumab in treatment of wet AMD: efficacy

30.3.2016

Raija Sipilä

Level of evidence = B

Bevacizumab and ranibizumab seem to have the same efficacy in maintaining visual acuity in the treatment of wAMD during 1-2 years of follow-up.

The Cochrane review [R1] aimed to investigate the ocular and systemic effects of, and quality of life associated with, intravitreally injected anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) for the treatment of neovascular age related macular degeneration (AMD) compared with no anti-VEGF treatment; and the relative effects of one anti-VEGF agent compared with another when administered in comparable dosages and regimens.

Inclusion criteria were: randomized controlled trial; patients with neovascular AMD, anti-VEGF treatment was compared with another treatment, sham injection, or no treatment; at least one year follow up. Excluded were studies comparing different doses; studies with aflibercept; and combination treatments.

Main outcome measure was best-corrected visual acuity (BCVA) at one year follow up; for comparisons the proportion of participants who gained 15 letters or more (3 lines) of BCVA in the study eye when BCVA was measured on a visual acuity chart with a LogMAR scale. Several secondary outcomes were listed including visual acuity, anatomical, quality of life, and safety outcomes.

Literature was search from CENTRAL, Medline, EMBASE, LILACS, mRCT, Clinical Trials, and WHO's ICTRP without date restriction until 27.3.2014. Search was supplemented with hand searches and contacts to pharmaceutical companies.

Altogether 4827 records, 403 clinical trials and 19 additional records were identified. Included in the review are 124 records from 12 studies and 7 ongoing trials with 5496 participants. The mean age of participants was 78–80 years except in one study and at least half of the participants were women. Two studies were international, 4 were conducted at USA, 2 in Austria, 2 in Great Britain, and 1 in France. Five trials included only participants with no previous treatment for choroidal neovascularization (CNV) or AMD. Among the included trials, there were variations in the types of eligible neovascular lesions (e.g., predominantly classic CNV, minimally classic CNV, or occult

CNV), lesion sizes, and baseline visual acuities of participants. Four comparisons of interventions were included: one study evaluated three doses of pegaptanib versus sham injection, three studies compared two doses of ranibizumab with sham injections or PDT, two studies compared bevacizumab with other treatments for AMD, and six studies were head-to-head trials of bevacizumab versus ranibizumab. Overall the included studies were at low risk of bias. One small study was not blinded. Follow up time varied from 12 to 24 months.

Bevacizumab (1.25 mg monthly or as needed) versus ranibizumab (0.5 mg monthly or as needed), follow up one year.

Gain of 15 letters or more visual acuity (6 studies, n=2446): RR 0.9 (95% confidence interval 0.73-1.11)

Loss of fewer than 15 letters of visual acuity (6 studies, n=2446): RR 1.00 (0.98-1.02)

Mean change in visual acuity (6 studies, n=2446): mean difference (MD) -0.51 (-1.64-0.62)

Mean change in central retinal thickness (4 studies, n=1995): MD -13.97um (-26.52 - -1.41)

No problems for each quality of life subscale (1 study, n=548): RR ranged for subscales between 0.96 (0.9-1.04) – 1.02 (0.89-1.17)

At least one serious adverse event (4 studies, n=2597): RR 1.27 (1.06-1.52)

Serious ocular adverse events <5/1000 for both, RR varied between 0.51 and 7.05.

Bevacizumab (1.25 or 1.0 mg) versus control, follow-up one year

Gain of 15 letters or more visual acuity (2 studies, n=159): RR 7.80 (2.44-24.98)

Loss of fewer than 15 letters of visual acuity (2 studies, n=159): RR 1.28 (1.09-1.50)

At least one serious adverse event (1 study, n=131): RR 2.03 (0.19-21.85)

Serious ocular adverse events (1 study, n=131): RR 1.86 (0.73-4.74)

Ranibizumab (0.3 or 0.5 mg) versus control, follow-up one year

Gain of 15 letters or more visual acuity (3 studies, n=1322): meta-analysis not performed due to heterogeneity (I²=80%). Assessed risk for the controls 59/1000 and for ranibizumab group 230/1000 (95% CI 93-566/1000)

Loss of fewer than 15 letters of visual acuity (3 studies, n=1322): RR 1.53 (1.41-1.64)

Mean change in visual acuity (3 studies, n=1322): MD 17.80 letters (15.95-19.65)

Change in mean vision-related quality of life (2 studies, n=1134): MD 6.69 (3.38-9.99)

At least one serious adverse event (2 studies, n=603): RR ranged from 0.17 to 2.08

Serious ocular adverse events (2 studies, n=603): RR ranged from 0.52 to 2.71.

- Study quality: High
- Applicability: Good

Meta-analysis [R2] evaluated the relative efficacy and safety of bevacizumab versus ranibizumab for the treatment of the neovascular form of age-related macular degeneration.

Included were randomized controlled trials with head-to-head comparisons of bevacizumab with ranibizumab in treatment of neovascular AMD. In addition inclusion criteria were: participants minimum age 50; and results on mean change in BCVA, mean change in central macular thickness, the proportion of patients with death, arteriothrombotic events, venous thrombotic events, and at least one serious systemic adverse event.

Literature search was conducted from PubMed, EMBASE and Cochrane Library until December 2013 and supplemented with manual search. Efficacy estimates were determined by comparing weighted mean differences in the change of BCVA and central macular thickness from baseline. Safety estimates were determined by calculating the risk ratio for rates of death, arteriothrombotic events, venous thrombotic events, and at least 1 serious systemic adverse event.

A total of 6 randomized controlled trials were included with 2612 patients (n=1292 in the bevacizumab group and 1320 in the ranibizumab group). Risk of bias was assessed to be low. Weighted mean difference between bevacizumab and ranibizumab in BCVA at 1 year or 2 years (2 studies) was -0.40 (95% confidence interval (CI) -1.48 to 0.69, p=0.47) and -1.16 (-2.82 to 0.51, p=0.17). Weighted mean difference for reducing central macular thickness at 1 year was 4.35 (0.92-7.78, p=0.01) favoring ranibizumab. The pooled risk ratios comparing the rates of serious systemic adverse events at 1 year and 2 years were slightly in favor of ranibizumab (1.24, 95% CI 1.04-1.48, p=0.02 and 1.20, 95%CI, 1.05-1.37, p=0.008, respectively). The rates of death, arteriothrombotic events, and venous thrombotic events did not differ statistically.

- Study quality: High
- Applicability: Good

Comment: Included are same studies than in the Cochrane review [R1]. When comparing the macula thickness, the weight of one small study was over 90%. When comparing BCVA results, the weight of CATT-study was 39%, otherways in was over 50%.

Meta-analysis and network meta-analysis [R3] aimed at quantifying the gain in visual acuity and serious side effects of ranibizumab, bevacizumab and aflibercept in AMD.

Included were randomised controlled trials comparing aflibercept, bevacizumab or ranibizumab against placebo or in a head-to head fashion with at least one year follow-up data. Outcome measures had to include visual acuity and serious side effects.

Literature was searched until June 2013 from (Pre)Medline, EMBASE, SCOPUS, Cochrane Library (until April 2013), Science Citation Index and reference lists were searched. Separate searches for efficacy and side effects were performed. Outcomes were 1-year follow-up data of visual acuity (letters gained) and serious (vascular death, any death, stroke, myocardial infarction, transient ischaemic attack) and thrombotic events.

Meta-analysis included 11 trials (8341 patients) assessing five active treatments: ranibizumab 0.3 mg (4 studies, n=1782), ranibizumab 0.5 mg (11 studies, n=3566), bevasizumab 1.25 mg (2 studies, n=882), aflibercept 0.5 mg (2 studies, n=597), and aflibercept 2 mg (2 studies, n=1220). Number of patients in placebo group was 294. Mean age of the participants was 76.7 years and 57% were women. Compared with placebo, all study treatments had a significantly higher percentage of letters gained.

Visual acuity, letters gained (%) compared to placebo

Ranibizumab 0.3 mg: 2.39% (95% confidence interval (CI) 1.59-3.19; p<0.001)

Ranibizumab 0.5 mg: 3.56% (2.58-4.13; p<0.001)

Bevacizumab 1.25 mg: 2.14% (0.47-3.82; p0.012)

Aflibercept 0.5 mg: 2.91% (0.99-4.82; p=0.003)

Aflibercept 2 mg: 3.44% (1.73-5.14; p<0.001).

In network analysis there were no statistically significant differences between the regimens.

- Study quality: Moderate
- Applicability: Good

Comment: Due to imperfect reporting, some of the data were imputed. Comparison with placebo is based on two small studies.

References

R1=Solomon SD, Lindsley K, Vedula SS ym. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database Syst Rev 2014;(8):CD005139
[PubMed](#)

R2=Chen G, Li W, Tzekov R ym. Bevacizumab versus ranibizumab for neovascular age-related macular degeneration: a meta-analysis of randomized controlled trials. Retina 2015;35:187-93 [PubMed](#)

R3=Schmid MK, Bachmann LM, Fäs L ym. Efficacy and adverse events of aflibercept, ranibizumab and bevacizumab in age-related macular degeneration: a trade-off analysis. Br J Ophthalmol 2015;99:141-6 [PubMed](#)

nak08697

Ranibizumab and bevacizumab in treatment of wet AMD: safety

30.3.2016

Raija Sipilä

Level of evidence = B

There seem to be no clinically significant short-term safety differences between ranibizumab and bevacizumab in the treatment of wAMD.

Cochrane review [R1] aimed to assess the systemic safety of intravitreal bevacizumab compared with intravitreal ranibizumab in patients with neovascular AMD.

Included were randomized controlled trials with head-to-head comparison of bevacizumab and ranibizumab in treatment of AMD. No other restriction for treatment regimens of participants was set. Primary endpoint was all-cause deaths; all serious systemic adverse events (SSAE); the sum of individuals affected by one or more SSAEs. Secondary outcomes were myocardial infarction (MI); stroke; arteriothrombotic event; serious haemorrhage; serious neutropenia; gastrointestinal perforation; serious infection; treatment related drug discontinuation.

Literature search was conducted from CENTRAL, Medline, EMBASE, mRCT, Clinical Trials, and WHO's ICTRP until 27.3.2014. Search was supplemented with hand search.

Total of 4827 records, 403 clinical trials and 19 conference abstracts were obtained. From 160 full text articles 25 records on 8 studies and 1 ongoing study (n=3665) were included. Six of the studies were completed and published. These studies had 1362 participants in bevacizumab group and 1383 in ranibizumab group. Follow up time was 4 years in 4 studies and 1 year in 2 studies. Two studies were completed but not published and one still ongoing (bevacizumab group n=482 and ranibizumab group n=438). Two were conducted in USA, 6 in Europe and 1 in India. The cardiovascular risk profile varied between the studies. Risk of bias could not be assessed for the unpublished studies. For the published studies the risk of bias was generally low.

Results

All-cause deaths (8 studies, n=3338, follow up 1-2 years): ranibizumab 34/1000, bevacizumab 37/1000, RR 1.10 (95% confidence interval 0.78-1.57)

All serious systemic adverse events (9 studies, n=3665): ranibizumab 222/1000, bevacizumab 240/1000, RR 1.08 (0.90-1.31), I²=41%

Infection (6 studies, n=3190): ranibizumab 37/1000, bevacizumab 50/1000, RR 1.34 (0.97-1.86)

Arteriothrombotic event (6 studies, n=3190): ranibizumab 35/1000, bevacizumab 32/1000, RR 0.92 (0.62-1.37)

Myocardial infarction (6 studies, n=3190): ranibizumab 14/1000, bevacizumab 12/1000, RR 0.84 (0.42-1.66)

Stroke (6 studies, n=3190): ranibizumab 11/1000, bevacizumab 9/1000, RR 0.83 (0.42-1.66)

gastrointestinal disorders (6 studies, n=3190): ranibizumab 16/1000, bevacizumab 29/1000, RR 1.82 (1.04-1.3.19)

In sensitivity analysis the exclusion of unpublished studies RR for death was 1.12 (95% CI 0.78-1.62; p=0.53) and for SSAEs RR 1.21 (1.06-1.37).

- Study quality: High
- Applicability: Good

Comment: One large study [R2] dominated the meta-analysis. Excluding it supported the finding, that there was no difference in total AEs. When unpublished results were excluded, risk of total AEs were higher in bevacizumab group compared to ranibizumab group. It was not possible to assess risk of bias in the unpublished studies.

Meta-analysis [R3] evaluated the relative efficacy and safety of bevacizumab versus ranibizumab for the treatment of the neovascular form of age-related macular degeneration.

Included were randomized controlled trials with head-to-head comparisons of bevacizumab with ranibizumab in treatment of neovascular AMD. In addition inclusion criteria were: participants minimum age 50; and reported results on mean change in BCVA, mean change in central macular thickness, the proportion of patients with death, arteriothrombotic events, venous thrombotic events, and at least one serious systemic adverse event.

Literature search was conducted from PubMed, EMBASE and Cochrane Library until December 2013 and supplemented with manual search. Efficacy estimates were determined by comparing weighted mean differences in the change of BCVA and central macular thickness from baseline. Safety estimates were determined by calculating the risk ratio for rates of death, arteriothrombotic events, venous thrombotic events, and at least 1 serious systemic adverse event.

A total of 6 randomized controlled trials were included with 2612 patients (n=1292 in the bevacizumab group and 1320 in the ranibizumab group). Risk of bias was assessed to be low. Weighted mean difference between bevacizumab and ranibizumab in BCVA at 1 year or 2 years (2

studies) was -0.40 (95% confidence interval (CI) -1.48 to 0.69, $p=0.47$) and -1.16 (-2.82 to 0.51, $p=0.17$). Weighted mean difference for reducing central macular thickness at 1 year was 4.35 (0.92-7.78, $p=0.01$) favoring ranibizumab. The pooled risk ratios comparing the rates of serious systemic adverse events at 1 year and 2 years were slightly in favor of ranibizumab (1.24, 95% CI 1.04-1.48, $p=0.02$ and 1.20, 95%CI, 1.05-1.37, $p=0.008$, respectively). The rates of death, arteriothrombotic events, and venous thrombotic events did not differ statistically.

- Study quality: High
- Applicability: Good

Comment: Same studies are included than in Cochrane review [\[R1\]](#).

Meta-analysis and network meta-analysis [\[R5\]](#) aimed at quantifying the gain in visual acuity and serious side effects of ranibizumab, bevacizumab and aflibercept in AMD.

Included were randomised controlled trials comparing aflibercept, bevacizumab or ranibizumab against placebo or in a head-to-head fashion with at least one year follow-up data. Outcome measures had to include visual acuity and serious side effects.

Literature was searched until June 2013 from (Pre)Medline, EMBASE, SCOPUS, Cochrane Library (until April 2013), Science Citation Index and reference lists were searched. Separate searches for efficacy and side effects were performed. Outcomes were 1-year follow-up data of visual acuity (letters gained) and serious (vascular death, any death, stroke, myocardial infarction, transient ischaemic attack) and thrombotic events.

Meta-analysis included 11 trials (8341 patients) assessing five active treatments: ranibizumab 0.3 mg (4 studies, $n=1782$), ranibizumab 0.5 mg (11 studies, $n=3566$), bevacizumab 1.25 mg (2 studies, $n=882$), aflibercept 0.5 mg (2 studies, $n=597$), and aflibercept 2 mg (2 studies, $n=1220$). Number of patients in placebo group was 294. Mean age of the participants was 76.7 years and 57% were women.

Compared with placebo, all study treatments had a significantly higher percentage of letters gained. Compared with placebo, serious side effects were higher in all active treatments: ranibizumab 0.3 mg 4.41% (95% confidence interval (CI) 3.42-5.40; $p<0.001$), ranibizumab 0.5 mg 5.33% (4.37-6.30; $p<0.001$), bevacizumab 1.25 mg 5.58% (3.567-7.6), aflibercept 0.5 mg 5.65% (3.28-8.02; $p<0.001$) and aflibercept 2 mg 5.29% (3.18-7.39; $p<0.001$). Compared with placebo, systemic thrombotic events occurred for 3.6% (2.69-4.56; $p<0.01$), 3.94% (3.02-4.86; $p<0.001$), 4.12% (2.27-5.97), and 3.94% (1.03-6.84; $p=0.008$), respectively. An estimate for aflibercept 2 mg could not be calculated. In the network analysis relationship between efficacy and serious side effects was assessed and no significant differences between the regimens were detected.

- Study quality: Moderate
- Applicability: Good

Comment: Due to imperfect reporting, some of the data were imputed. Comparison with placebo is based on two small studies.

A cohort study [R4] within a randomized clinical trial [R2] assessed risk factors for scar in eyes treated with ranibizumab or bevacizumab for neovascular age-related macular degeneration (AMD).

For the original trial (CATT, n=1185) patients with active choroidal neovascularization (CNV) secondary to AMD and no scar at foveal center on color fundus photography (CFP) or fluorescein angiography (FA) at enrollment were included. Other inclusion criteria were age >50 years and visual acuity between 20/25 and 20/320 in the study eye. To the cohort study only patients without scar at baseline and with gradable photographs at both 1 and 2 years were included (n=1059). Eyes were assigned to ranibizumab or bevacizumab treatment for 2 years to 1 of 3 dosing regimens: monthly injection, monthly evaluation with pro re nata injections, or 3 monthly injections and thereafter pro re nata injections. CFP and FA scans were obtained at baseline, 1 year, and 2 years. Masked readers assessed CFP and FA. Scars were classified as fibrotic or nonfibrotic. Main outcome measure was scar formation.

Scar developed in 339 of 1059 eyes (32%) by 1 year and in 480 (45.3%) by 2 years. Fibrotic scars developed in 24.7% of eyes, and nonfibrotic scars developed in 20.6% of eyes. Baseline characteristics associated with greater risk of scarring were predominantly classic CNV (adjusted hazard ratio aHR, 3.1; 95% CI, 2.4-3.9) versus occult CNV, blocked fluorescence (aHR, 1.4; CI, 1.1-1.8), foveal retinal thickness >212 μm (aHR, 2.4; CI, 1.7-3.6) versus <120 μm , foveal subretinal tissue complex thickness >275 μm (aHR, 2.4; CI, 1.7-3.6) versus ≤ 75 μm , foveal subretinal fluid (aHR, 1.5; CI, 1.1-2.0) versus no subretinal fluid, and subretinal hyperreflective material (SHRM) (aHR, 1.7; CI, 1.3-2.3) versus no SHRM. Eyes with elevation of the retinal pigment epithelium had lower risk (aHR, 0.6; CI, 0.5-0.8) versus no elevation. Drug, dosing regimen, and genotype had no statistically significant association with scarring.

- Study quality: Moderate
- Applicability: Good

References

R1=Moja L, Lucenteforte E, Kwag KH ym. Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. Cochrane Database Syst Rev 2014;(9):CD011230 [PubMed](#)

R2=Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG ym. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012;119:1388-98 [PubMed](#)

R3=Chen G, Li W, Tzekov R ym. Bevacizumab versus ranibizumab for neovascular age-related macular degeneration: a meta-analysis of randomized controlled trials. Retina 2015;35:187-93 [PubMed](#)

R4=Daniel E, Toth CA, Grunwald JE ym. Risk of scar in the comparison of age-related macular degeneration treatments trials. Ophthalmology 2014;121:656-66 [PubMed](#)

R5=Schmid MK, Bachmann LM, Fäs L ym. Efficacy and adverse events of aflibercept, ranibizumab and bevacizumab in age-related macular degeneration: a trade-off analysis. Br J Ophthalmol 2015;99:141-6 [PubMed](#)

nak08698

Aflibercept in treatment of wet AMD: efficacy

30.3.2016

Raija Sipilä

Level of evidence = B

Monthly or less frequent intravitreal injections of aflibercept (0.5-2 mg) seem to be as effective as monthly injected ranibizumab (0.5 mg) in maintaining visual acuity.

Two phase-3 studies (VIEW 1, VIEW 2) [R1] compared monthly and every-2-month dosing of intravitreal aflibercept injection with monthly ranibizumab for patients with neovascular age-related macular degeneration (AMD).

The studies were double-masked (unmasked investigator performed the study drug or sham injection), multicenter, parallel-group, active-controlled and randomized.

Inclusion criteria were age >50 years with active subfoveal choroidal neovascularization (CNV) lesions (any subtype) secondary to AMD, juxtafoveal lesions with leakage affecting the fovea also were allowed; CNV comprising at least 50% of total lesion size; best corrected visual acuity (BCVA) between 73 and 25 Early Treatment Diabetic Retinopathy Study chart (ETDRS) letters (20/40 – 20/320 Snellen equivalent). Patients with prior treatment for AMD in the study eye; total lesion size > 12 disc area; presence of other causes of CNV or ocular disease; presence of contraindications to ranibizumab were excluded.

VIEW 1 was conducted in USA and Canada and VIEW 2 in Europe, the Middle East, Asia and Latin America. A total of 2419 patients (VIEW 1 n=1217 and VIEW 2 n=1240) were randomized to intravitreal aflibercept 0.5 mg monthly (0.5q4, n=304/311), 2 mg monthly (2q4, n=304/313), 2 mg every 2 months after 3 initial monthly doses (2q8, n=303/313) (to maintain masking, sham injections were given at the interim 4-week visits after week 8), or ranibizumab 0.5 mg monthly (Rq4, n=306/303). The patients in VIEW 2 study had lightly more severe AMD at baseline and worse general health.

The primary end point was noninferiority (margin of 10%) of the aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 letters on ETDRS chart). Secondary end points included mean change in BCVA, gaining >15 letters, change in Visual Function Questionnaire score, change in CNV area on fluorescein angiography, retinal thickness and persistent fluid. The margin for clinical equivalence was 5%. Endpoint assessment

was performed every 4 weeks. Both full analysis and per protocol analysis were conducted. The drop-out rate for aflibercept groups were 7.1% (VIEW1) and 10.7% (VIEW2). The respective figures for ranibizumab groups were 7.2% and 8.9%.

Proportion of patients maintaining vision at week 52 for the 2q4, 0.5q4, and 2q8 regimens were 95.1%, 95.9%, and 95.1% for VIEW 1, and 95.6%, 96.3%, and 95.6% for VIEW 2. For monthly ranibizumab the proportion was 94.4% in both studies. Mean change in BCVA was +8.7 letters for Rq4 group, +9.3 for 2q4 group, and +8.4 for 2q8 group. In VIEW1 study 2q4 group was statistically significantly superior to other groups, gaining 10.9 letters. In integrated analysis of the two studies all aflibercept regimens produced similar improvements in anatomic measures.

- Study quality: High
- Applicability: Moderate

Comment: Around 95% of study population in the VIEW1-study were Caucasians. VIEW2-were partly done in Europe, with around 20% of study population being of Asian origin. Study was sponsored by Regeneron Pharmaceuticals and Bayer HealthCare. Sponsors were involved in planning the study protocol, analyzing the results, and writing the manuscript.

The aim was to report disease-specific quality of life (QoL) data from VIEW 1 and VIEW 2 studies [R2]. The methods are described in more detail in the above abstract [R1].

This analysis included patients who received intravitreal aflibercept 2.0 mg every 8 weeks after 3 initial monthly doses (2q8; n=607) or ranibizumab 0.5 mg every 4 weeks (Rq4; n=595).

The 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) was a secondary outcome for the studies. It was administered at baseline and at weeks 12, 24, 36, and 52. The assessments were conducted by masked trained interviewers by telephone in VIEW 1 and face-to-face in VIEW 2. Mean change from baseline to week 52 in composite score and in subscale scores were compared between the groups. Clinically meaningful change in subscore was defined as 4- to 6-point change. Full analysis was used: included were subjects who received study medication and had at least one post-baseline assessment. Last observation was carried forward.

Mean baseline NEI VFQ-25 composite scores were 69.6 for 2q8 group and 71.8 for Rq4 group in VIEW 1, and 71.3 and 72.9 for VIEW 2, respectively. Mean change from baseline to 52 weeks in composite score (pooled data) showed meaningful improvement only in patients who gained 5 ETDRS letters or more (7.3 and 7.8 points for 2q8 and Rq4). Mean change from baseline to 52 weeks was similar for ranibizumab and aflibercept across all 12 subscales, with the greatest improvements noted for mental health and general vision (9.0-11.6 points, both treatments, both studies). Statistically significant difference between the groups were in 3 subscores (not defined) in

VIEW 1 study and none in VIEW 2. Improvement of 4 points or more (both treatments, both studies) also was observed for subscales near vision, distance vision, role difficulties, and dependency. The improvements were attained by 6 months.

- Study quality: High
- Applicability: Moderate

Comment: Around 95% of study population in the VIEW1-study were Caucasians. VIEW2-were partly done in Europe, with around 20% of study population being of Asian origin. Study was sponsored by Regeneron Pharmaceuticals and Bayer HealthCare. Sponsors were involved in planning the study protocol, analyzing the results, and writing the manuscript.

The purpose of the study was to determine efficacy and safety of intravitreal aflibercept in patients with AMD during a second year of variable dosing after a first-year fixed-dosing period [R3].

The study is follow-up for VIEW 1 and VIEW 2 studies [R1], therefore methods are described in more detail above.

Two randomized, double-masked, active-controlled, phase 3 trials. At baseline 2457 patients were randomised to receive 0.5 mg intravitreal ranibizumab every 4 weeks (Rq4), 2 mg aflibercept every 4 weeks (2q4), 0.5 mg aflibercept every 4 weeks (0.5q4), or 2 mg aflibercept every 8 weeks (2q8) after 3 monthly injections. A total of 2235 patients entered the follow-up study and 2063 (91.0%) completed it. During weeks 52 through 96, patients received their original dosing assignment using an as-needed regimen with defined retreatment criteria and mandatory dosing at least every 12 weeks. Retreatments criteria were new persistent fluid on optical coherent tomography (OCT), increase in central retinal thickness of 100 µm or more, loss of 5 or more ETDRS letters in conjunction with persistent fluid on OCT, new-onset classic neovascularization, new or persistent leak on fluorescein angiography, and new macular hemorrhage.

Main outcome measures were proportion of eyes at week 96 that maintained BCVA (lost <15 letters from baseline) and change from baseline in BCVA. Secondary outcomes were mean change in central retinal thickness and number of study injections.

Proportions of eyes maintaining BCVA across treatments were 94.4% to 96.1% at week 52 and 91.5% to 92.4% at week 96 (difference of aflibercept groups compared to ranibizumab group -0.1 - +0.8%). Mean BCVA gains were 8.3 to 9.3 letters at week 52. At week 96 gain were 7.9, 7.6, 6.6, and 7.6 letters for Rq4, 2q4, 0.5q4, and 2q8 groups representing 1 to 2 letter loss compared to week 52. Proportion of patients who gained 15 letters or more was 31.6%, 31.2%, 28.1%, and 33.4% for Rq4, 2q4, 0.5q4 and 2q8 groups. Proportions of eyes without retinal fluid decreased from week 52 (60.3% to 72.4%) to week 96 (44.6% to 54.4%), and more 2q4 eyes were without

fluid at weeks 52 and 96 than Rq4 eyes (difference of 10.4%, 95%confidence interval (CI) 4.9-15.9] and 9.0% [95%CI, 3.0-15.1]). Patients received on average 16.5, 16.0, 16.2, and 11.2 injections during the 96 weeks period and 4.7, 4.1, 4.6, and 4.2 injections during weeks 52 through 96 in the Rq4, 2q4, 0.5q4, and 2q8 groups, respectively.

- Study quality: High
- Applicability: Moderate

Comment: Around 95% of study population in the VIEW1-study were Caucasians. VIEW2-were partly done in Europe, with around 20% of study population being of Asian origin. Study was sponsored by Regeneron Pharmaceuticals and Bayer HealthCare. Sponsors were involved in planning the study protocol, analyzing the results, and writing the manuscript.

Meta-analysis and network meta-analysis [R4] aimed at quantifying the gain in visual acuity and serious side effects of ranibizumab, bevacizumab and aflibercept in AMD.

Included were randomised controlled trials comparing aflibercept, bevacizumab or ranibizumab against placebo or in a head-to head fashion with at least one year follow-up data. Outcome measures had to include visual acuity and serious side effects.

Literature was searched until June 2013 from (Pre)Medline, EMBASE, SCOPUS, Cochrane Library (until April 2013), Science Citation Index and reference lists were searched. Separate searches for efficacy and side effects were performed. Outcomes were 1-year follow-up data of visual acuity (letters gained) and serious (vascular death, any death, stroke, myocardial infarction, transient ischaemic attack) and thrombotic events.

Meta-analysis included 11 trials (8341 patients) assessing five active treatments: ranibizumab 0.3 mg (4 studies, n=1782), ranibizumab 0.5 mg (11 studies, n=3566), bevacizumab 1.25 mg (2 studies, n=882), aflibercept 0.5 mg (2 studies, n=597), and aflibercept 2 mg (2 studies, n=1220). Number of patients in placebo group was 294. Mean age of the participants was 76.7 years and 57%were women.

Visual acuity, letters gained (%) compared to placebo

Ranibizumab 0.3 mg: 2.39% (95% confidence interval (CI) 1.59-3.19; p<0.001)

Ranibizumab 0.5 mg: 3.56% (2.58-4.13; p<0.001)

Bevacizumab 1.25 mg: 2.14% (0.47-3.82; p0.012)

Aflibercept 0.5 mg: 2.91% (0.99-4.82; p=0.003)

Aflibercept 2 mg: 3.44% (1.73-5.14; p<0.001).

- Study quality: Moderate
- Applicability: Moderate

Comment: Due to imperfect reporting, some of the data were imputed. Comparison with placebo is based on two small studies. Aflibercept results are based on the View1 and VIEW2 studies [\[R1\]](#).

References

R1=Heier JS, Brown DM, Chong V ym. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012;119:2537-48 [PubMed](#)

R2=Yuzawa M, Fujita K, Wittrup-Jensen KU ym. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. *Ophthalmology* 2015;122:571-8 [PubMed](#)

R3=Schmidt-Erfurth U, Kaiser PK, Korobelnik JF ym. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology* 2014;121:193-201 [PubMed](#)

R4=Schmid MK, Bachmann LM, Fäs L ym. Efficacy and adverse events of aflibercept, ranibizumab and bevacizumab in age-related macular degeneration: a trade-off analysis. *Br J Ophthalmol* 2015;99:141-6 [PubMed](#)

nak08699

Aflibercept in treatment of wet AMD: safety

30.3.2016

Raija Sipilä

Level of evidence = C**Monthly or less frequent intravitreal injections of aflibercept (0.5-2 mg) may be as safe as monthly injected ranibizumab (0.5 mg) in the treatment of wAMD**

Two phase-3 studies (VIEW 1, VIEW 2) [R1], [R2] compared monthly and every-2-month dosing of intravitreal aflibercept injection with monthly ranibizumab for patients with neovascular age-related macular degeneration (AMD).

The studies were double-masked (unmasked investigator performed the study drug or sham injection), multicenter, parallel-group, active-controlled and randomized.

Inclusion criteria were age ≥ 50 years with active subfoveal choroidal neovascularization (CNV) lesions (any subtype) secondary to AMD, juxtafoveal lesions with leakage affecting the fovea also were allowed; CNV comprising at least 50% of total lesion size; best corrected visual acuity (BCVA) between 73 and 25 Early Treatment Diabetic Retinopathy Study chart (ETDRS) letters (20/40–20/320 Snellen equivalent). Patients with prior treatment for AMD in the study eye; total lesion size > 12 disc area; presence of other causes of CNV or ocular disease; presence of contraindications for ranibizumab were excluded.

VIEW 1 was conducted in USA and Canada and VIEW 2 in Europe, the Middle East, Asia and Latin America. A total of 2419 patients (VIEW 1 $n=1\ 217$ and VIEW 2 $n=1\ 240$) were randomized to intravitreal aflibercept 0.5 mg monthly (0.5q4, $n=304/311$), 2 mg monthly (2q4, $n=304/313$), 2 mg every 2 months after 3 initial monthly doses (2q8, $n=303/313$) (to maintain masking, sham injections were given at the interim 4-week visits after week 8), or ranibizumab 0.5 mg monthly (Rq4, $n=306/303$).

The primary end point was noninferiority (margin of 10%) of the aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 letters on ETDRS chart). Secondary end points included mean change in BCVA, gaining >15 letters, change in Visual Function Questionnaire score, change in CNV area on fluorescein angiography, retinal thickness and persistent fluid. Endpoint assessment was performed every 4 weeks. Both full analysis and per protocol analysis were conducted. The drop-out rate for combined aflibercept

groups were 7.1% (VIEW1) and 10.7% (VIEW2). The respective figures for ranibizumab group was 7.2% and 8.9%.

Proportion of patients maintaining vision at week 52 for the 2q4, 0.5q4, and 2q8 regimens were 95.1%, 95.9%, and 95.1% for VIEW 1, and 95.6%, 96.3%, and 95.6% for VIEW 2. For monthly ranibizumab the proportion was 94.4% in both studies. In integrated analysis of the two studies all aflibercept regimens produced similar improvements in anatomic measures.

Number (percentage) of patients with at least 1 ocular serious adverse event was 10 (3.3) for Rq4 group, 7 (2.3) for 2q4 group, 6 (2.0) for 0.5q4 group and 2 (1.0) for 2q8 group in VIEW 1 study. The figures in VIEW 2 study were 9 (3.1), 6 (1.9), 5 (1.7), and 9 (2.9), respectively. The combined data for both studies showed a rate of treatment-emergent serious adverse events (eye disorders, endophthalmitis, procedural complications, and increased intraocular pressure) per1000 injections of 1.1, 0.8, 0.1, and 0.2 for the Rq4, 2q4, 0.5q4, and 2q8 groups, respectively. Overall incidence of serious systemic adverse events (range VIEW 1 13.2–18.8% and VIEW 2 8.9–12.5%), specific arterial thromboembolic end points as set forth by the Anti-Platelet Trialists' Collaboration (range VIEW 1 0.7–2.3% and VIEW 2 1.3–2.6%), and deaths was similar between aflibercept and ranibizumab. Among the aflibercept treatment groups, there was no evidence of a dose-response for adverse events.

- Study quality: Moderate
- Applicability: Good

Comment: Around 95% of study population in the VIEW1-study were Caucasians. VIEW2-were partly done in Europe, with around 20% of study population being of Asian origin. Study was sponsored by Regeneron Pharmaceuticals and Bayer HealthCare. Sponsors were involved in planning the study protocol, analyzing the results, and writing the manuscript.

The purpose of the study [R3] was to determine efficacy and safety of intravitreal aflibercept in patients with AMD during a second year of variable dosing after a first-year fixed-dosing period.

The study is a follow-up for VIEW 1 and VIEW 2 studies [R1], therefore methods are described in detail above.

Two randomized, double-masked, active-controlled, phase 3 trials. At baseline 2457 patients were randomised to receive 0.5 mg intravitreal ranibizumab every 4 weeks (Rq4), 2 mg aflibercept every 4 weeks (2q4), 0.5 mg aflibercept every 4 weeks (0.5q4), or 2 mg aflibercept every 8 weeks (2q8) after 3 monthly injections. A total of 2 235 patients entered the follow-up study and 2 063 (91.0%) completed it. During weeks 52 through 96, patients received their original dosing assignment using an as-needed regimen with defined retreatment criteria and mandatory dosing at least every 12

weeks. Retreatment criteria were new persistent fluid on optical coherent tomography (OCT), increase in central retinal thickness of 100 µm or more, loss of 5 or more ETDRS letters in conjunction with persistent fluid on OCT, new-onset classic neovascularization, new or persistent leak on fluorescein angiography, and new macular hemorrhage.

Main outcome measures were proportion of eyes at week 96 that maintained BCVA (lost <15 letters from baseline) and change from baseline in BCVA. Secondary outcomes were mean change in central retinal thickness and number of study injections.

Proportions of eyes maintaining BCVA across treatments were 94.4% to 96.1% at week 52 and 91.5% to 92.4% at week 96. Mean BCVA gains were 8.3 to 9.3 letters at week 52. At week 96 gains were 7.9, 7.6, 6.6, and 7.6 letters for Rq4, 2q4, 0.5q4, and 2q8 groups representing 1 to 2 letter loss compared to week 52.

Most common ocular adverse events were conjunctival hemorrhage (range 23.7–29.9%), retinal hemorrhage (13.6–16.2%), reduced visual acuity (11.3–13.0%), eye pain (8.9–12.1%), vitreous detachment (7.7–10.0%), and increased intraocular pressure (6.2–10.8%) from baseline to week 96. Intraocular inflammation was reported for 1.5%, 1.1%, 0.8%, and 0.5% for Rq4, 2q4, 0.5q4 and 2q8 groups. Serious ocular adverse events occurred for 4.4%, 3.6%, 3.2%, and 3.9%, respectively. The figures for serious non-ocular adverse events were 24.5%, 21.4%, 25.3%, and 25.2%. These events included atrial fibrillation, myocardial infarction, pneumonia, fall, congestive heart failure, coronary artery disease, TIA, cerebrovascular accident, COPD and osteoarthritis. Percentage of specific arterial thromboembolic end points as set forth by the Anti-Platelet Trialists' Collaboration was 3.2% for Rq4 group and 2.4% for 2q4, 3.8% for 0.5q4, and 3.6% for 2q8. The percentage of nonfatal myocardial infarction ranged from 1.0 to 2.0% and nonfatal stroke from 0.5 to 0.8%. The percentage of deaths was 2.7%, 2.1%, 3.2%, and 3.3% for the groups.

- Study quality: Moderate
- Applicability: Good

Comment: Around 95% of study population in the VIEW1-study were Caucasians. VIEW2-were partly done in Europe, with around 20% of study population being of Asian origin. The AE's were not predefined as primary or secondary end-points, although they were reported. Study was sponsored by Regeneron Pharmaceuticals and Bayer HealthCare. Sponsors were involved in planning the study protocol, analyzing the results, and writing the manuscript.

Meta-analysis and network meta-analysis [R4] aimed at quantifying the gain in visual acuity and serious side effects of ranibizumab, bevacizumab and aflibercept in AMD.

Included were randomised controlled trials comparing aflibercept, bevacizumab or ranibizumab against placebo or in a head-to head fashion with at least one year follow-up data. Outcome measures had to include visual acuity and serious side effects.

Literature was searched until June 2013 from (Pre)Medline, EMBASE, SCOPUS, Cochrane Library (until April 2013), Science Citation Index and reference lists were searched. Separate searches for efficacy and side effects were performed. Outcomes were 1-year follow-up data of visual acuity (letters gained) and serious (vascular death, any death, stroke, myocardial infarction, transient ischaemic attack) and thrombotic events.

Meta-analysis included 11 trials (8 341 patients) assessing five active treatments: ranibizumab 0.3 mg (4 studies, n=1 782), ranibizumab 0.5 mg (11 studies, n=3 566), bevacizumab 1.25 mg (2 studies, n=882), aflibercept 0.5 mg (2 studies, n=597), and aflibercept 2 mg (2 studies, n=1 220). Number of patients in placebo group was 294. Mean age of the participants was 76.7 years and 57% were women.

Compared with placebo, all study treatments had a significantly higher percentage of letters gained. Compared with placebo, serious side effects were higher in all active treatments: ranibizumab 0.3 mg 4.41% (95% confidence interval (CI) 3.42–5.40; $p<0.001$), ranibizumab 0.5 mg 5.33% (4.37–6.30; $p<0.001$), bevacizumab 1.25 mg 5.58% (3.567–7.6), aflibercept 0.5 mg 5.65% (3.28–8.02; $p<0.001$) and aflibercept 2 mg 5.29% (3.18–7.39; $p<0.001$). Compared with placebo, systemic thrombotic events occurred for 3.60% (2.69–4.56; $p<0.01$), 3.94% (3.02–4.86; $p<0.001$), 4.12% (2.27–5.97), and 3.94% (1.03–6.84; $p=0.008$), respectively. An estimate for aflibercept 2 mg could not be calculated. In the network analysis relationship between efficacy and serious side effects was assessed.

- Study quality: Moderate
- Applicability: Good

Comment: Due to imperfect reporting, some of the data were imputed. Comparison with placebo is based on two small studies. Aflibercept results are based on the View1 and VIEW2 studies [R4].

References

R1=Heier JS, Brown DM, Chong V ym. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012;119:2537-48 [PubMed](#)

R2=Yuzawa M, Fujita K, Wittrup-Jensen KU ym. Improvement in vision-related function with intravitreal aflibercept: data from phase 3 studies in wet age-related macular degeneration. *Ophthalmology* 2015;122:571-8 [PubMed](#)

R3=Schmidt-Erfurth U, Kaiser PK, Korobelnik JF ym. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology 2014;121:193-201 [PubMed](#)

R4=Schmid MK, Bachmann LM, Fäs L ym. Efficacy and adverse events of aflibercept, ranibizumab and bevacizumab in age-related macular degeneration: a trade-off analysis. Br J Ophthalmol 2015;99:141-6 [PubMed](#)

nak08700

Treatment of wAMD patients with photodynamic therapy (PDT) combined with ranibizumab

30.3.2016

Raija Sipilä

Level of evidence = B**Treatment of wAMD patients with photodynamic therapy (PDT) combined with ranibizumab does not seem to improve visual acuity compared to treatment with ranibizumab alone.**

A systematic review and meta-analysis [R1] compared the efficacy and safety of combination of ranibizumab with photodynamic therapy (PDT) and ranibizumab monotherapy in the treatment of age-related macular degeneration (AMD).

Included were randomized controlled trials comparing ranibizumab with PDT and ranibizumab monotherapy in patients with active choroidal neovascularization secondary to AMD. In addition at least one of the following outcome measures had to report: best-corrected visual acuity (BVCA), central retinal thickness, number of treatments and ocular or systemic adverse events. Not published conference abstracts were excluded. The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, Pubmed, and Embase were searched until September 2013. In addition hand-searches were conducted. Methodological quality of the literatures was evaluated according to the Jadad Score.

From a total of 181 potential studies 7 were included in the systematic review and of them four were included in meta-analysis. Three studies were performed in USA and one each in UK, Italy, Austria, and Denmark. Mean age varied between 71 and 80 years. Duration of follow up was 12 months except in one study with 6 months follow up. Four of the studies were assessed to be of high quality. Two of the studies had over 100 participants per treatment group, the others had 2 to 30 participants per group. There were clinical heterogeneity among the studies. Dose of ranibizumab was 0.5 mg in all studies but the frequency of the injection varied and dose of PDT varied.

Ranibizumab monotherapy group had a better mean BCVA change vs baseline at month 12 compared with that of the combination treatment group weighted mean difference (WMD) -2.61; 95% CI, -5.08 - -0.13; p=0.04. In sensitivity analysis, after the removal of one study due to clinical heterogeneity, the difference between the two groups showed no significant difference WMD -2.29; 95% CI, -4.81 - 0.23; p=0.07. Weighted mean difference for central retinal thickness reduction was

-4.13 μ m; 95% CI, -25.88 - 17.63, p=0.71. As major adverse events, the differences in the number of eye pain, endophthalmitis, hypertension and arterial thromboembolic events were not significant between the two groups, and the incidence of serious adverse events in the two groups was very low. Relative risk (RR) for eye pain was 1.38 (95% CI 0.81-2.35), for endophthalmitis 0.53 (0.05-5.80), and for arterial thromboembolic events 0.81 (0.28-2.28).

- Study quality: High
- Applicability: Good

Comment: There was heterogeneity regarding participating patients and treatments among the included studies. 5 out of 7 studies were small. 4 studies, included in the meta-analysis, were assessed as high quality. The AE results were based on 2 studies.

Randomized, controlled double-blind trial [R2] compared combination therapy of ranibizumab plus PDT vs ranibizumab monotherapy in the treatment of AMD.

Inclusion criteria were age >50 years, subfoveal choroidal neovascularization (CNV) secondary to AMD, visual acuity Snellen equivalent 20/40-20/320, lesion consisted of >50% active CNV. Exclusion criteria were laser photocoagulation, intravitreal steroids or PDT in the study eye within 30 days, prior external-beam radiation therapy, vitrectomy or transpupillary thermotherapy, or surgery in the eye within 2 months prior to intravitreal anti-VEGF treatment.

Consecutive eligible patients from one study center were randomized 1:1 to monotherapy ranibizumab (plus sham PDT, N=21) or combination therapy (ranibizumab plus single standard-fluence verteporfin PDT at baseline, n=19). The ranibizumab dose was 0.3 mg monthly three times and thereafter up to 12 months as needed based on prespecified criteria. Minimum interval was 28 days.

Outcome measures were changes in mean BCVA, retreatment rates, and safety evaluation (all adverse events). Intention-to-treat analysis was performed only for safety data.

Majority of patients were female (monotherapy 67% and combination therapy 68%), mean age was 78 and 79 years, patients with prior PDT was 19% and 36.8%, and percentage of patients with CNV composition of occult without classic was 47.6% vs 78.9%. Dropout rate was 7.5%.

At month 6 the mean improvement in BCVA from baseline was 10.2 \pm 1.8 in monotherapy group, and 8.5 \pm 2.5 in combination therapy group. At month 12 the corresponding figures were 7.5 \pm 2.9 and 9.0 \pm 2.8, respectively. There was a trend for lower number of retreatments in combination therapy group but none of the between-group differences reached statistical significance. No

serious adverse events were reported, ocular adverse events were reported for 11 patients in monotherapy group and 10 in combination therapy group.

- Study quality: Moderate
- Applicability: Moderate

Comment: Efficacy was calculated by per protocol, not by intention to treat. There were between groups differences at the baseline. Retreatment rates were reported as one of the primary outcome measures, although they were preregistered as secondary outcomes (clinicaltrials.gov). The study was sponsored by Novartis Pharma AG, who also sponsored writing of the manuscript.

References

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R2=Hatz K, Schneider U, Henrich PB ym. Ranibizumab plus verteporfin photodynamic therapy in neovascular age-related macular degeneration: 12 months of retreatment and vision outcomes from a randomized study. *Ophthalmologica* 2015;233:66-73 [PubMed](#)