Vascular-Endothelial-Growth-Factor-Inhibitors (anti-VEGF) for Diabetic Macular Oedema

Systematic Review

Agencija za kvalitetu i akreditaciju u zdravstvu

Ludwig Boltzmann Institut
Health Technology Assessment

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Summary

Background and research question: Diabetic macular oedema (DME) is the leading cause of vision loss in the working age population in developed countries. Therapeutic approaches so far have been laser photocoagulation (current gold standard), intravitreal steroid injections and vitrectomy. In this report we address the question whether an alternative treatment approach, namely vascular-endothelial-growth-factor-inhibitors (anti-VEGF), leads to better clinical outcomes and fewer adverse events than current treatments in patients with clinically manifest diabetic macular oedema.

photocoagulation, glucocorticoids and vitrectomy are current treatments of DME

is anti-VEGF better and safer?

Methods: We performed a systematic literature search in common medical and HTA-databases and synthesised the evidence according to the GRADE-methodology.

systematic literature search + GRADE

Results: Overall quality of evidence for efficacy of anti-VEGF in the management of DME is moderate, while quality of evidence for safety is very low. In a proportion of patients (on average 25%) VEGF-inhibitors result in better visual acuity than in patients treated with glucocorticoids or with laser photocoagulation. However, the number of injections required for long-term improvement as well as general long-term efficacy is unknown. While neither study demonstrated serious safety problems, evidence is not sufficient to regard the products as safe in patients with DME. Concerning the different products, there is slightly stronger evidence supporting ranibizumab compared to bevacizumab, however due to the lack of head-to-head trials, this does not suggest superiority of a single product.

quality of evidence moderate for efficacy and very low for safety

in ¼ of patients short term improvement of visual acuity; safety unclear; no superiority of single product

Conclusion: For some patients with DME, VEGF-inhibitors seem to be a more effective short-term treatment than alternative therapies. Evidence is not of sufficient quality to confirm safety. A decision on financing should take into account the high price-difference between the products and the fact that many studies are still ongoing.

treatment is beneficial, enormous price differences to be considered

1 Anti-vascular endothelial growth factor (anti-VEGF) in the management of diabetic macular oedema

1.1 Background

DME leading cause of vision loss

Diabetic macular oedema (DME) which is a frequent manifestation of diabetic retinopathy is the leading cause of vision loss in the working age population in developed countries.

many risk factors

vision impairment strongly related to diabetes control

Within 20 years almost all patients with diabetes type I and 60% with type II diabetes develop diabetic retinopathy [1]. The presence of DME has been associated with longer duration of diabetes (any type), insulin use, high glycosylated haemoglobin levels, proteinuria, hypertension and male gender [2]. Prolonged oedema results in irreversible damage and permanent loss of vision, hence visual impairment among people with diabetes increases with age. However, vision impairment due to DME is very much related to how well diabetes is controlled.

Austria: 130,000 adults with diabetes, ~23% have retinopathy; prevalence DME: 3%-6% in diabetic patients

According to WHO estimates, in Austria the prevalence of diabetes in adults is 130,000 (2.1%). A European study identified a retinopathy prevalence of 23% in the Austrian sub-sample of patients with diabetes [3]. The prevalence of DME is uncertain (international figures range from 3% to 6% of all patients with diabetes aged 18+) [4]. This would relate to roughly 4,000 to 7,800 persons with DME in Austria. A large epidemiological study identified macular oedema in 26% of those with diabetic retinopathy [5].

breakdown of blood-retinal barrier and vascular permeability play major role

The pathogenesis of DME is multifactorial. It is mainly caused by a breakdown of the blood-retinal barrier, leading to accumulation of fluid and plasma constituents (e.g. lipoproteins) within the inner layers of macula. This is accompanied by increased vascular permeability due to the release of a protein called vascular endothelial growth factor (VEGF) [6].

therapy so far: laser, glucocorticoids, vitrectomy

mostly stabilisation, not improvement of visual acuity

Therapeutic approaches so far have been laser photocoagulation, intravitreal steroid injections and vitrectomy. Among those, laser photocoagulation has been the gold standard [7]. However, while laser photocoagulation may preserve vision it has not been successful in improving it [4]. Reviews on intravitreal steroid injections have demonstrated temporal improvement on visual acuity but this is accompanied with an increased risk of raised intraocular pressure and development of cataracts [4]. Finally, RCTs on vitrectomy have shown little effect in patients with DME except for specific subgroups [4].

1.2 Anti-VEGF for diabetic macular oedema

alternative treatment: anti-VEGF

As an alternative treatment for DME anti-vascular-endothelial growth factors (anti-VEGF) have been introduced. Different types of anti-VEGF are available which have in common that they inhibit VEGF angiogenic activity

by binding to the VEGF protein and thus preventing its receptor activation [8]. Ultimately, this should reduce vascular permeability and growth and hence, DME.

3 products: pegaptanib (Macugen®),

Pegaptanib (Macugen®, Eyetech Pharmaceuticals Inc.) is a pegylated aptamer that targets only the VEGF 165 isoform and is currently approved for the treatment of neovascular age-related macular degeneration (AMD) [8, 9].

bevacizumab (Avastin®),

Bevacizumab (Avastin®, Genentech Inc.) is a full-length humanised antibody that binds to all types of VEGF. It is used in and licensed for tumour therapy [8, 9].

ranibizumab (Lucentis®),

Ranibizumab (Lucentis®, Genentech Inc.; marketed by Novartis in Europe) comes from the same parent molecule as bevacizumab, however, it is a humanised monoclonal antibody *fragment* that binds all active forms of VEGF-A and is currently approved for AMD and DME [8].

only RBZ licensed for DME, IVB because of lower price used off-label

In summary, only ranibizumab has been approved for the treatment in DME in Europe. Ranibizumab and bevacizumab were both developed by Genentech (now part of Roche) but Roche-Genentech has not sought a licence for eye use of bevacizumab [4]. However, due to the high price of ranibizumab, bevacizumab has regularly been used off-label while experimental studies are underway. Because bevacizumab has been approved in tumour therapy (in a higher dose), it has to be divided into smaller doses for ocular indications.

regular treatment in monthly intervals until stable improvement, otherwise termination

Treatment with anti-VEGF in DME needs to be done in regular intervals until the maximum improvement in visual acuity is achieved (stability after several monthly controls during treatment). If no improvement is realised treatment should be stopped. Re-treatment is recommended if visual acuity decreases again after successful treatment [10]. Optimal treatment intervals are still subject to evaluation and may differ between the different anti-VEGF products due to their different molecule-sizes and varying half-time. Currently monthly intervals are recommended.

intravitreal application under sterile conditions

VEGF inhibitors need to be applied intravitreally under sterile conditions. Because regular re-treatment is required, there is an increased long-term risk of infections leading to endophtalmitis.

1.3 Indication and therapeutic aim

clinical significant DME defined by retinal thickening

Macular oedema is defined as retinal thickening and oedema involving the macula. As has been outlined by the Early Treatment Diabetic Retinopathy Study (ETDRS) group, clinically significant macular oedema presents the following characteristics: retinal thickening within 500 μm of the centre of the fovea, hard exudates within 500 μm of the fovea if associated with adjacent retinal thickening, or one or more areas of retinal thickening at least 1500 microns in diameter that are within one disc diameter (1500 microns) of the fovea [7, 11].

several diagnostic methods

Diagnostic methods are sit lamp examination with a contact lens, stereo photography, flourescein angiography and optical coherence tomography [8].

Therapeutic aim of anti-VEGF injections in diabetic macular oedema is to improve and stabilize quality of vision and, ultimately, to increase quality of life which is severely threatened by visual loss (e.g. severe limitation in daily activities like reading, watching TV or driving a car, increased risk of falls).

therapeutic aim: improvement of quality of life by better visual acuity

As has been outlined in a previous decision support document [12], the main parameter to measure vision is visual acuity (VA) which expresses the ability to identify small letters with high contrast at a specified distance. Visual acuity ranges from 0.01 to2.5 (logMAR).

parameters: visual acuity (VA),

Therapeutic success regarding visual acuity is evaluated by measuring best corrected visual acuity (BCVA) before and after treatment. Usually, ETDRS (Early Treatment of Diabetic Retinopathy Study)-charts are used for defining visual acuity. Another frequently used chart to evaluate visual acuity is the Snellen-chart.

BCVA, ETDRS-letters, Snellen-lines

Changes are commonly expressed in logMAR (logarithm of minimal angle of resolution) lines. 1 ETDRS-line is equivalent to 0.1 logMAR. In other words, the magnitude of visual acuity expressed in logMAR decreases with increased visual acuity. Alternatively, changes are expressed in ETDRS-letters.

expressed in logMAR

For people to experience meaningful improvement, visual acuity needs to be improved by a minimum of two to three lines or 10 to 15 letters [4]. Hence, statistically significant changes in visual acuity are not necessarily clinically relevant. Additionally, from the outcome parameters measured in the studies, mean values are of less interest than the proportion of patients gaining clinically relevant improvement in vision [4, 8]. Moreover, visual acuity does not represent quality of vision in general (such as seeing objects with poor contrast, how much effort is needed to see clearly etc.).

meaningful improvement: 2-3 lines or 10-15 letters

only of limited value for defining overall quality of vision

For assessing overall vision-related quality of life, specific quality of life questionnaires that assess visual functioning (such as VFQ-25) are available. It has been demonstrated that a change between 3.6 and 15 points on the VFQ-25 corresponds to a three line change in visual acuity in patients with age related macular degeneration. Hence, for a clinically relevant improvement a mean increase of at least 3.6 points is required [13].

VFQ-25 for assessing vision-related quality of life

In terms of safety, intraocular adverse events (AE) caused by any injection (e.g. endophtalmitis), intraocular problems related to anti-VEGF and systemic adverse events due to leakage of anti-VEGF into the systemic circulation need to be analysed.

local or systemic adverse events possible

1.4 Estimated volumes and costs

According to the Austrian application document it is estimated that there will be about 12,000 intravitreal applications of anti-VEGF for the defined population in 2011 in Austria.

12,000 injections required

The unit price for ranibizumab (10 mg/ml injection solution) will be € 954,64 from March 2011 onwards [14]. Bevacizumab (25 mg/ml) costs 368 €. The price of pegaptanib is unknown. Due to the required division into smaller doses the price of a single bevacizumab injection is manifold cheaper than a single ranibizumab injection. Assuming that bevacizumab and ranibizumab are divided into 18-20 doses and three doses respectively, a

price per injection ranibizumab is 16-fold the price of a bevacizumab injection

single injection of bevacizumab costs 20 € and the price of a single ranibizumab is 320 €.

2 Literature search and selection of literature

2.1 Research question

PICO-question

Does the intravitreal application of vascular-endothelial-growth-factor-inhibitors (anti-VEGF) in patients with clinically significant diabetic macular oedema lead to better clinical outcomes (improved visual acuity) and fewer (systemic and local) adverse events (AE) than alternative treatments with laser photocoagulation, intravitreal application of glucocorticoids or vitrectomy?

2.2 Inclusion criteria

inclusion criteria for study selection

Inclusion criteria for study selection are presented in table 2.2-1.

Table 2.2-1: Inclusion criteria

Population	Patients with clinically significant diabetic macular oedema
Intervention	Intravitreal application of vascular endothelial growth factor (VEGF) inhibitors (+ laser)
Control intervention	a) Laser photocoagulation b) Intravitreal application of glucocorticoids c) Vitrectomy d) VEGF inhibitors in combination with laser e) VEGF inhibitors in combination with glucocorticoids
Outcomes	a) Clinical outcomes: improvement of visual acuity, quality of life b) Adverse events: systemic (cardiovascular diseases/events…) and local: ocular procedure-related (endophtalmitis, injuries,…) or drug-related (inflammatory processes, bleedings,…) events
Study design	For efficacy: RCTs For safety: comparative observational studies and large-scale single-arm studies (e.g. registries) Follow up: ≥24 weeks

2.3 Literature search

systematic literature search in data bases and websites

The systematic literature search was performed on January 25th and 26th, 2011 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- NHS EED-DARE-HTA (INAHTA)

An additional search for assessments was undertaken on January 27th, 2011 on the following websites:

- Canadian Agency for Drugs and Technologies in Health (http://www.cadth.ca/index.php/en/home)
- NIHR Health Technology Assessment programme (http://www.hta.ac.uk/)
- NHS Institute for Health and Clinical Excellence (http://www.nice.org.uk/)
- WHO Health Evidence Network (http://www.euro.who.int/en/what-we-do/data-and-evidence/health-evidence-network-hen)

858 sources via systematic search

handsearch + manufacturer: 116

in total:974 references

No search restrictions (e.g. in terms time period/type) were applied in the first systematic search stage. For abstract scanning, only English and German references from 2000 to 01/2011 were considered. After removing all duplicates, 858 references from the systematic search were available. One additional source was retrieved from manufacturers' information. Via handsearch we identified another 115 sources so that finally 974 references were available. The search strategies can be found in the Appendix

2.4 Selection of literature

literature search

Overall, 974 references were available. Relevant references were selected by two persons independently. Different selection results were discussed in order to achieve consensus. A third person was involved in cases of uncertainty. The selection process is presented in figure 2.4-1.

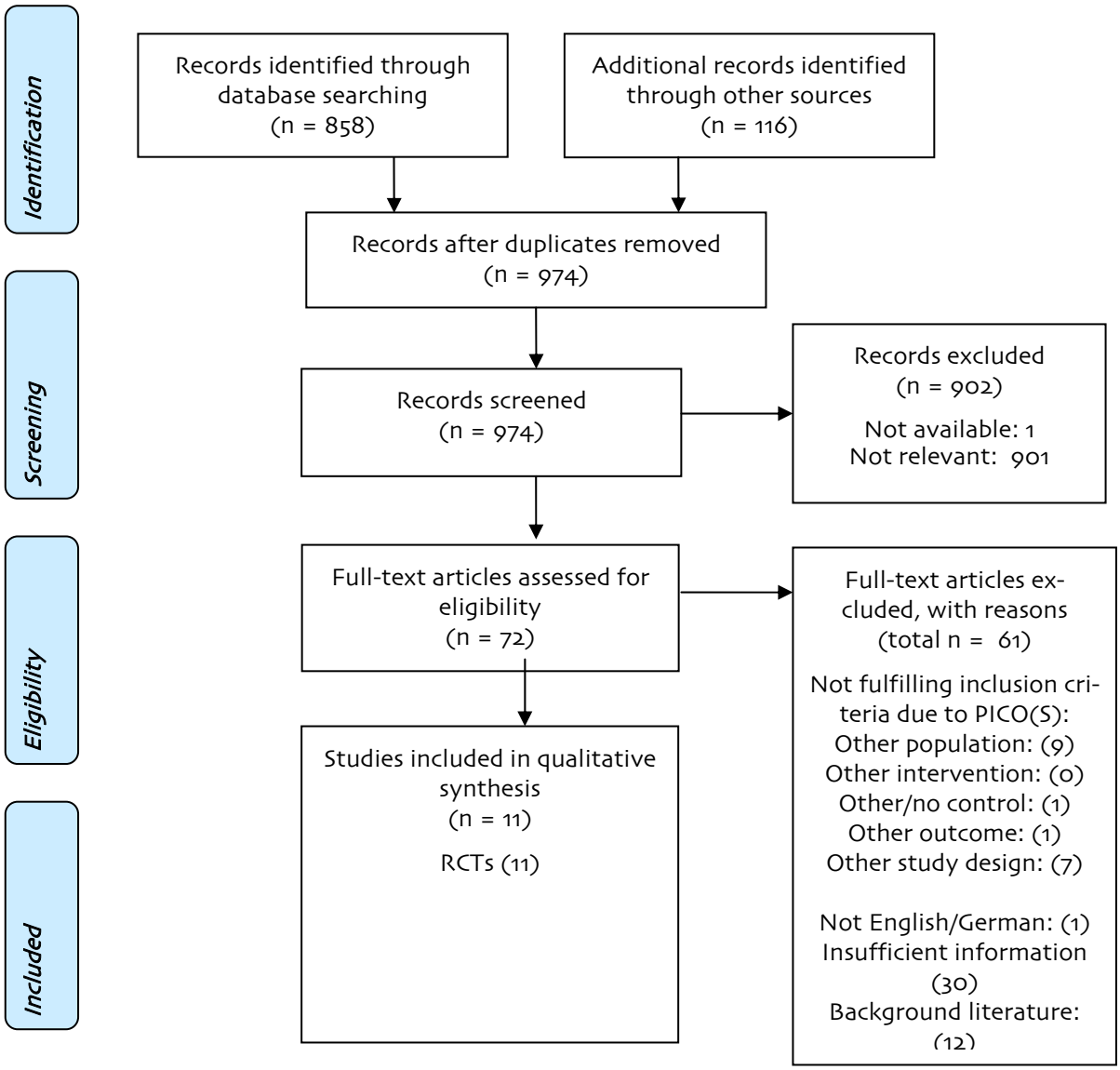

Figure 2.4-1: Selection process according to PRISMA flow chart

3 Study quality assessment

quality assessment method

Assessment of the internal validity of studies was done by two researchers independently. Different results were discussed in order to achieve consensus. A third person was involved in cases of uncertainty. The internal manual of the LBI-HTA describes the quality criteria in detail [15].

4 Data extraction

data extraction

Data extraction was done by a single researcher. A second researcher independently double-checked the data for correctness and completeness.

4.1 Description of study results

IVB: 6 RCTs

RBZ: 4 RCTs

Pegaptanib: 1 RCT

For answering the research question eleven randomised controlled trials (RCT) were available. Six RCTs [16-21] are on bevacizumab from which one [19] is used for evaluating adverse events only, because it compares two doses of bevacizumab only without a placebo or alternative therapy. Four RCTs [22-24] have evaluated efficacy and safety of ranibizumab and one trial is on pegaptanib [25]. None of the observational studies fulfilled our inclusion criteria.

IVB: patients with refractory DME or therapy-naive

comparator: sham-injections, triamcinolone, laser or combination of those with IVB

28 to 150 eyes randomised

Study characteristics and results from RCTs on bevacizumab are presented in table 4.1-1. Three studies on bevacizumab include patients with refractory DME and the remainder treated therapy-naive patients or both. Patients were mainly around 60 years of age. Half of the studies compared bevacizumab with triamcinolone injections or a combination of bevacizumab and triamcinolone and in another half photocoagulation or a combination of photocoagulation plus bevacizumab was the comparator. One study compared bevacizumab with sham-injections. There was no study available that compared intravitreal bevacizumab injections with vitrectomy. Study size ranged from 28 to 150 eyes randomised and participants were followed for six to 12 months. None of the bevacizmab-studies was industry-sponsored.

RBZ: patients with previous treatment but not necessarily failure

comparator: sham-injection, laser, combination laser + RBZ

126 to 854 eyes randomised

pegaptanib: comparison with sham

Study characteristics and results from RCTs on ranibizumab (four trials) and pegaptanib (1 trial) are presented in table 4.1-2. Experimental studies on ranibizumab included patients in who the previous treatment had to be at least three to six months in the past, while in the pegaptanib-study previously untreated patients were included. The mean age of the study population was slightly above 60. Ranibizumab-studies compared anti-VEFG treatment with either sham-injections or photocoagulation or with a combination of ranibizumab injections plus laser. One study compared ranibizumab plus prompt or deferred laser with steroid injections or laser only. The comparator in the pegaptanib study was sham injection. Again, no study compared intravitreal ranibizumab or pegaptanib with vitrectomy. Study size for the ranibizumab and the pegaptanib studies was on average larger than in the bevacizumab studies, namely between 126 and 854 eyes. The follow-up pe-

riod was six to twelve months. All of the ranibizumab-studies and the pegaptanib-study were industry-sponsored.

extracted outcome parameters: mean visual acuity

We extracted the following outcome parameter from the studies: firstly, data on visual acuity were extracted in the way they were presented in the study. In the majority of studies mean change in visual acuity described as best corrected visual acuity (BCVA) logMAR or mean changes in ETDRS-letters were presented. Some publications additionally showed mean baseline and follow-up values.

% of patients who achieved ≥15 letters or 2-3 lines improvement, quality of life

Secondly, we extracted information on the proportion of patients with at least 10 or 15 letters or two to three lines improvement and on the proportion of patients with 10/15letters or two/three lines worsening. Thirdly, data on vision-related quality of life were extracted which were available in one study only.

safety: local and systemic AE

Finally, we extracted data on adverse events reported. On the one hand, these included local AE: ocular procedure-related events such as endophtalmitis or injuries, local drug-related events such as inflammatory processes or local bleedings. On the other hand, reported systemic adverse events such as cardiovascular events or increased blood pressure were extracted.

anatomical changes not extracted

Data on anatomical changes such as central macular thickness that were presented in all studies were not extracted because they were regarded as irrelevant for patients (see PICO-question chapter 2.2).

Table 4.1-1: Results from RCTs on bevacizumab in diabetic macular oedema (significant results in bold)

Author, year, reference number	Paccola (2008) [16]	Ahmadieh (2008) [17]	Soheilian (2009) [18]	Lam (2009) ([19]	Solaiman (2010) [20]	Michaelides (2010) [21]
Country	Brazil	Iran	Iran	Hong Kong	Egypt	UK
Sponsor	Non-industry	Non-industry	Non-industry	Non-industry	Non-industry	Non-industry
Product/Intervention	Arm 1:IVB (1.5mg) single dose	Arm 1: IVB (1.25mg) ≤3 doses	Arm 1: IVB (1.25mg) re-treatment at 12 ws if required	Arm 1: IVB (1.25mg) 3 doses	Arm 1: IVB (1.25mg) single dose	Arm 1: IVB (1.25mg) ≥3 to 9 doses
Comparator	Arm 2: IVT (4mg) single dose	Arm 2: IVB (1.25mg) followed by 2 doses + IVT (2mg) Arm 3: sham-injection	Arm 2: IVB (1.25 mg) +IVT (2 mg), re-treatment if required Arm 3: MPC (re-treatment as re-quired)	Arm 2: IVB (2.5mg) 3 doses	Arm 2: MPC once Arm 3: MPC +IVB (1.25mg) single dose	Arm 2: MPC (re-treatment if required)
Study design	RCT	RCT	RCT	RCT	RCT	RCT
No. of eyes (patients) No. randomised per arm	28(28) 14/14	115 (101) 41/37/37	150 (129) 50/50/50	52 (52) 26/26	62 (48) 19/21/22	80 (80) 42/38
Inclusion criteria	Refractory DME ETDRS BCVA: 0.3 (20/40 Snell. equival.) or worse CMT: ≥300µm	Refractory DME VA: 20/40 or worse, CMT not stated	Untreated DME VA: 20/40-20/300	DME treated ≥6ms/untreated VA (logMAR): 1.3 and better CMT: ≥250µm	Untreated diffuse DME CMT: ≥350µm	Refractory DME VA: 6/12-6/60 CMT: ≥270µm
Age of patients per group	66/67	60 (mean age)	61/62/61	65/66	56/57/59	65/64
Follow up	24 ws (6 ms)	24 ws (6 ms)	24 ws/6 ms (prim. outcome) 36 ws (9 ms) (sec. outcome)	24 ws (6 ms)	24 ws (6 ms)	24 ms (this study = 12-ms re-sults)
Drop-out rate	1/28 (IVB) 1/28 (IVT)	Not stated	6/50 (IVB) 12/50 (IVB/IVT) 7/50 (MPC)	3/26 (IVB 1.25mg) 1/26 (IVB 2.5mg)	Not stated	0/42 (IVB) 2/38 (MPC)
Efficacy						
LogMAR BCVA **Within arm**: mean at base-line/follow-up (mean dif-ference, p-value)	24 ws ± 1) 0.9375/0.9125 (-0.025, n.s.) 2) 0.9366/0.9233 (-0.0133, n.s.)	24 ws ±± 1) -0.18 2) -0.21 3) -0.03	24ws; 36 ws ±± 1) 0.23;0.28 (**p 0.001/0.001**) 2) 0.07;0.04 (p 0.178/0.057) 3) 0.01;0.01 (p 0.858/0.865)	24 ws ± 1) 0.63/0.52 (-0.11; **p 0.018**) 2) 0.60/0.47 (-0.13; **p 0.003**)	24 ws 1) 0.84/0.82 (-0.02, n.s.) 2) 0.84/0.85 (+0.01, n.s.) 3) 0.83/0.74 (-0.09, n.s.)	1 yr* 1) 55.7/61.3 (+5.6/+8# letters) 2) 54.6/50.0 (-4.6/-0.5# letters)
Between arm: mean dif-ference (p value)	IVB/IVT:-0.1 (n.s.)	Sham/IVB: 0.21 **(p 0.010)** Sham/IVB + IVT: 0.24 **(p 0.006)** IVB/IVB +IVT: 0.02 (p 0.999)	IVB/IVB+IVT: 0.16 (24 ws) 0.24 (36 ws) IVB/MPC: 0.22 (24 ws) 0.27 (36 ws) (P 24 ws: **0.012**; 36 ws: 0.053)	IVB1/IVB2: -0.02 (p 0.79)	IVB/MPC: 0.03 (n.s.) MPC+IVB/IVB: -0.07 (n.s.)	IVB/MPC: +11.3 letters **(p 0.006)** median change: IVB/MPC: +8.5 letters **(p 0.002)**

Author, year, reference number	Paccola (2008) [16]	Ahmadieh (2008) [17]	Soheilian (2009) [18]	Lam (2009) ([19]	Solaiman (2010) [20]	Michaelides (2010) [21]
% 2 lines gain±± % unchanged % 2 lines loss			24ws;36 ws 31/21/11; 37/25/15 69/64/66;59/54/68 0/15/23;4/21/19 (p 24 ws: **0.014**; 36 ws 0.164)			
% ≥15 ETDRS letters gain % ≥10 ETDRS letters gain % <15 ETDRS letters loss % ≥30 ETDRS letters loss						11.9/5.3 (p 0.43) 31.0/7.9 (**p 0.01**) 97.6/73.7 **(p 0.01)** 0/5.3 (p 0.22)
Adverse events						
Local (yes/no) Systemic (yes/no) SAE (yes/no)	Yes No No	Yes No Yes	Yes No Yes	No No Yes	No Not stated Not stated	Yes: 20(42)/8(38) Yes: 4(42)/3(38) Yes: 3(42)/7(38)
Description of SAE per arm		Death 0(41)/0(37)/**1**(37) Vitreous haemorrhage: 0(41)/**1**(37)/0(37)	Death 0(50)/**2**(50)/**2**(50) Progress to high-risk PDR: 4(50)/3(50)/3(50)	Foot gangrene requiring amputation **1**(26)/0(26)		Foot ulcer 1(42)/1(38) Cholecystectomy 1(42)/0(38) Fall 0(42)/1(38) Worsening angina 0(42)/1(38) CVI 0(42)/1(38) IOP ≥45mmHg 1(42)/0(38) Vitreous haemorrhage 0(42)/1(38)
Description of AE 1) Transient chamber reaction 2) Ocular hypertension 3) Lens opacity 4) Retinal neovasc. 5) Early PDR 6) Retinal detachment	2) significant increase of IOP in IVT-group at week 4	1) 1(41)/0(37)/0(37) 2) 0(41)/3(37)/0(37) 3) 0(41)/0(37)/0(37) 4) 0(41)/0(37)/0(37) 5) 1(41)/0(37)/0(37)	1) 10(50)/9(50)/0(50) 2) 0(50)/8(50)/0(50) 3) 0(50)/4(50)/1(50) 4) 4(50)/2(50)/3(50) 5) 1(50)/4(50)/3(50) 6) 0(50)/2(50)/2(50)			

*AE: adverse events; BCVA: best corrected visual acuity; diff.: difference; CMT: central macular thickness; DME: diabetic macular edema; ETDRS: Early Treatment Diabetic Retinopathy Study; IVB: intravitreal bevacizumab; IVT: intravitrial triamcinolone; logMAR: logarithm of the minimal angle of resolution; MPC: macular laser photocoagulation; ms: months; n.s.: not significant; PDR: proliferative diabetic retinopathy; RCT: randomised controlled trial; SAE: serious adverse event; VA: visual acuity; ws: weeks; *ETDRS letters; ±ETDRS chart; ±±Snellen chart; # median change*

Table 4.1-2: Results from RCTs on ranibizumab and pegaptanib in diabetic macular oedema (significant results in bold)

Author, year, reference number	**Nguyen (2009) [22]**	**Massin (2010) [23]**	**DRCRN (2010) [24]**	**Novartis study (2011) [26]**	**MDRSG (2005) [25]**
Country	USA (multicenter)	Europe (multicenter)	USA (multicenter)	Europe+Australia+Canada+NZ	International (multicenter)
Sponsor	Genentech	Novartis	Genentech+Allergan	Novartis	Eyetech Pharmaceuticals, Pfizer
Product/Intervention	Arm 1: RBZ (0.5mg) 4 doses	Arm 1: RBZ (0.3-0.6mg) Arm 2: RBZ (0.5-1.0mg) 3 monthly	Arm 1: RBZ (0.5mg) ≥3 doses + prompt MPC Arm 2: RBZ (0.5mg) ≥3 doses + deferred MPC	Arm 1: RBZ (0.5mg) ≥3 doses + sham MPC;	Arm 1: Pegaptanib (PG) (0.3mg) Arm 2:PG (1mg) Arm 3:PG (3mg) ≥3 doses
Comparator	Arm 2: MPC baseline + ms 3 Arm 3: RBZ (0.5mg) 2 doses + MPC	Arm 3: sham	Arm 3: IVT (4mg) every 4 ws + prompt MPC Arm 4: sham + prompt MPC	Arm 2: RBZ (0.5mg) ≥3 doses + MPC Arm 3: MPC + sham RBZ	Arm 4: sham
Study design	RCT	RCT	RCT	RCT	RCT
No. of eyes (patients) No. randomised per arm	126(126) 42/42/42	151 (151) 102/49	854 (691) 187/188/186/293	345 (345) 116/118/111	172 (172) 44/44/42/42
Inclusion criteria	DME treated >3ms/untreated VA: 20/40 to 20/320 CMT: ≥250 µm	DME treated >6ms/ untreated VA: 20/40 to 20/160 CMT: ≥300 µm	DME treated >4ms/untreated VA: 20/32 to 20/320 CMT: 250 µm	Focal or diffuse DME >3 to 6ms treated/untreated VA: 20/32 to 20/160	DME untreated VA: 20/50 to 20/230 CMT: not stated
Age of patients per group	62/62/62	63/63/65	62/64/62/63	63/64/64	62/63/61/64
Follow up	24 ws (6 ms)	12 ms	Prim. outc: 12 ms (3 yrs planned)	12 ms	36 ws (9 ms)
Drop-out rate	5/42 (RBZ) 4/42 (MPC) 2/42 (RBZ + MPC)	10/102 (RBZ groups) 9/49 (sham)	16/187 (RBZ + MPC) 19/188 (RBZ + def. MPC) 10/178 (IVT + MPC) 19/293 (sham + MPC)	14/116 (RBZ + sham MPC) 15/118 (RBZ + MPC) 13/111 (MPC+ sham RBZ)	0/44 (PG 0.3mg) 0/42 (PG 1mg) 3/42 (PG 3mg) 6/41 (sham)
Efficacy					
BCVA (ETDRS letters) **Within arm**: mean at baseline/follow-up (mean difference)	6 ms 1) +7.24 letters 2) -0.43 letters 3) +3.8 letters	1 yr 1) 59.2/70.9 (+11.8 letters) 2) 61.2/70 (+8.8 letters) 3) 61.1/59.7 (-1.4 letters)	1 yr 1) +9 letters 2) +9 letters 3) +4 letters 4) +3 letters :	1 yr 1) 64.7/71.5 (+6.8 letters) 2) 63.4/69.7 (+6.4 letters) 3) 62.6/63.4 (+0.9 letters)	9 ms 1) +4.7 letters 2) +4.7 letters 3) +1.1 letters 4) +0.4 letters
Between arm: mean difference (p value)	RBZ/MPC: 6.81 (**p 0.001**) RBZ/RBZ + MPC: 3.44 (p 0.08) RBZ + MPC/MPC: 4.23 (n.s.)	RBZ1/sham: 13.4 **(p <0.0001)** RBZ2/sham: 10.6 **(p <0.0001)**	RBZ+prompt MPC/MPC: 5.8 (**p 0.001**) RBZ+defer. MPC/MPC: 6 (**p 0.001**) IVT+prompt MPC/MPC: 1.1 (p 0.31)	RBZ/MPC: 6.2 (**p <0.001**) RBZ+MPC/MPC: 5.4 (**p0.004**)	0.3mg PG/sham:4.3 (**p 0.04**) 1mg PG/sham: 4.3 (**p 0.05**) 3mg PG/sham: 0.7 (p0.55)

Author, year, reference number	Nguyen (2009) [22]	Massin (2010) [23]	DRCRN (2010) [24]	Novartis study (2011) [26]	MDRSG (2005) [25]
% ≥3 lines gain % ≥2 lines gain	22/0/8 RBZ/MPC: +22%-points (**p 0.002**) RBZ+MPC/MPC: +14%-points (p?) 46/5/30 RBZ/MPC: +41%-points (**p 0.00004**) RBZ+MPC/MPC: +16%-points (**p 0.007**)				18/14/7/7
% ≥10 letters gain % ≥10 letters loss % ≥15 letters gain % ≥15 letters loss		37/25/9 0/5/12 RBZ1/sham: **(p <0.0001)** RBZ2/sham: **(p 0.001)** 18/15/5 0/3/10 RBZ1/sham (**p 0.0001**) RBZ2/2sham (**p 0.0037**)	20/19/12/13 RR1*/MPC: 1.84 (**p 0.001**) RR2/ MPC: 1.68 (**p 0.001**) RR3/ MPC: 1.21 (p 0.16) 2/1/6/5 RR1/ MPC: 0.24 (**p 0.001**) RR2/ MPC: 0.24 (**p 0.001**) RR3/ MPC: 1.08 (p 0.75) 30/28/21/15 RR1/ MPC: 2.09 (**p 0.001**) RR2/ MPC: 1.89 (**p 0.001**) RR3/ MPC: 1.43 (p 0.07) 2/2/8/8 RR1/ MPC: 0.21 (**p 0.009**) RR2/ MPC: 0.28 (**p 0.01**) RR3/ MPC: 1.02 (p 0.95)	37/43/16 RBZ/MPC: (**p<0.0001**) RBZ+MPC/MPC: (**p<0.001**) 4/4/13 23/23/8 RBZ/MPC: (**p 0.0032**) RBZ+MPC/MPC: (**p 0.0021**) 1/3/8	
Visual functioning (VFQ-25) mean baseline/follow-up Difference between groups				1) 72.8/77.8 (5.0) 2) 74.1/79.5 (5.4) 3) 73.5/74.1 (0.6) RBZ/MPC: 4.1 (**p 0.0137**) RBZ+MPC/MPC: 4.7 (**p 0.0041**)	
Adverse events					
Local (yes/no) Systemic (yes/no) SAE (yes/no)	Yes No Yes	Yes 80(102)/28(49) Yes 14(102)/6(49) Yes	Yes Yes Yes 6(187)/2(188)/13(178)/6(293)	Yes 49(115)/51(120)/43(110) Yes 67(115)/55(120)/68(110) Yes 33 (115)/24 (120)/22(110)	Yes 38(44)/34(42)/37(42)/30(41) No Yes 6(44)/2(42)/13(42)/6(41)

Author, year, reference number	Nguyen (2009) [22]	Massin (2010) [23]	DRCRN (2010) [24]	Novartis study (2011) [26]	MDRSG (2005) [25]
Description of SAE per arm	Death (0(42)/0(42)/**1**(42) Vitreous haemorrhage 1(42)/4(42)/3(42)	Vitreous haemorrhage 1(51)/0(51)/0(49) Retinal ischaemia 0(51)/**1**(51)/0(49) Retinal artery occlusion 0(51)/1(51)/0(49) Endopthalmitis 1(51)/1(51)/0(49) Retinal detachment 0(51)/0(51)/1(49) Metabolism/nutrition 2(51)/1(51)/1(49) Infections 1(51)/1(51)/3(49) Urinary bladder cancer 1(51)/0(51)/0(49) Arterial thromboembolic events 0(51)/3(51)/2(49) Non-ocular haemorrhage 1(51)/1(51)/0(49)	Ocular vascular event 1(187)/0(188)/2(186)/1(273) Endophtalmitis 1(187)/1(188)/0(186)/0(273) Retinal detachment 0(187)/1(188)/0(186)/0(273) Vitrectomy 0(187)/3(188)/0(186)/7(273) Vitreous haemorrhage 3(187)/4(188)/2(186)/15(273) Non-fatal MI 1(RBZ)/2(IVT)/3(sham) Non-fatal cerebrovasc. event 3(RBZ)/1(IVT)/5(sham) Vascular death 7(RBZ)/2(IVT)/4(sham) Any ATC event 11(RBZ)/5(IVT)/10(sham)	Death 2(115)/2(120)/2(110) Cardiac disorders 8(115)/4(120)/4(110) Gastrointestinal disorders 3(115)/3(120)/2(110) Infections 6(115)/3(120)/3(110) Metabolism and nutrition 4(115)/2(120)/3(110) Nervous system 5(115)/1(120)/2(110) Respiratory, thoracic 4(115)/2(120)/2(110) Vascular disorders 4(115)/2(120)/3(110) Ocular study eye (0(115)/2(120)/2(110) Ocular fellow eye 3(115)/1(120)/2(110)	Endophtalmitis 0.15% per injection or 0.8 % per subject
Description of AE 1) Ocular hypertension 2) Blood pressure increase 3) Non-ocular AE 4) Glaucoma surgery 5) Cardiac disorders		2) 4(51)/5(51)/5(49) 3) 64(102)/32(49)	1) 10(187)/5(188)/70(178)/16(293) 4) 0(187)/0(188)/0(178)/0(293) Number of events per injection 2) 16(710 RBZ)/6(369 IVT)/0(319 sham) 5) 17(710 RBZ)/13(369 IVT)/12(319 sham)		

*AE: adverse event; BCVA: best corrected visual acuity; CMT: central macular thickness; DME: diabetic macular edema; ETDRS: early treatment of diabetic retinopathy study group; IVT: Intravitreal Triamcinolone; MPC: macular laser photocoagulation; ms: months; PG: Pegaptanib; Prim. outc.: Primary outcome; RCT: randomised controlled trial; RBZ: Ranibizumab; SAE: serious adverse event; ws: weeks; yrs.: years; *difference in proportion from sham /relative risk*

4.2 Efficacy

Table 5-1 presents the efficacy results of anti-VEGF compared to alternative treatments.

Bevacizumab

Current evidence on the efficacy of intravitreal bevacizumab (IVB) compared to sham injections shows that IVB significantly improves mean visual acuity, however the single study available does not provide information on the proportion of patients in which gains in letters was clinically relevant and on long-term effects.

IVB vs. sham: improved mean VA in 6 months

Studies that compare IVB with laser photocoagulation have shown higher and clinically relevant gains (up to one year follow-up) in mean visual acuity in IVB-patients than in those who received photocoagulation (partly significant). A higher proportion of patients (max. 37%) in the IVB-groups achieved a clinically relevant gain in letters; however significance of this difference was unclear.

IVB vs. laser: partly significant and relevant improvement of mean VA

Studies did not demonstrate a difference between IVB and intravitreal steroids, yet there is only one trial with short follow-up and a small study population available.

IVB vs. glucocorticoids: no difference

Similarly, studies did not demonstrate a significant and clinically relevant difference between IVB alone or with triamcinolone. The proportion of patients that gained at least two Snellen lines is lower in patients that receive IVB plus triamcinolone and more people in the combined group lost ≥2 lines, yet the difference is not significant.

IVB vs. IVB + glucocort.: no difference

Finally, no difference was demonstrated when comparing IVB alone or in combination with laser photocoagulation. Yet, quality of evidence in this case is very low and the outcome 'percentage of patients that gain/loose ≥10 or 15 letters' has not been measured.

IVB vs. IVB + laser: no difference, important outcomes not measured

No information is available on the improvement in vision related quality of life in bevacizumab studies.

no info on quality of life

Ranibizumab

A single and high quality study on the efficacy of intravitreal injections of ranibizumab (RBZ) compared to sham injections showed that after one year RBZ significantly improved mean visual acuity and the percentage of patients gaining at least 15 letters was significantly higher in the RBZ-group (max. 18%) than in the sham-injection group. Vice versa, the proportion of those who lost ≥15 letters was lower in the RBZ-group than in the sham-injection group. Those who received the lower RBZ-dose did better than those with the higher dose.

RBZ vs. sham: more patients (max. 18%) achieved ≥15 letters

Additionally, studies demonstrated a significant but not clinically relevant higher mean visual acuity in the RBZ groups compared to laser photocoagulation. However, clinically relevant efficacy has been demonstrated by showing that around 23% compared to a maximum of 8% gained at least 15 letters in the RBZ and photocoagulation groups respectively. This difference is statistically significant. Fewer patients in the RBZ group compared to those who received photocoagulation lost ≥15 letters, yet significance is unclear and only one study was available on that outcome parameter. Finally, pa-

RBZ vs. laser: more patients (max. 23%) achieved ≥15 letters

higher quality of life in RBZ group

tients in the RBZ-group achieved a higher improvement in vision related quality of life than those in the laser group.

RBZ vs. glucocort.: no data

No evidence is available on the comparison between RBZ and intravitreal steroids or on the comparison between RBZ alone or in combination with intravitreal steroids.

RBZ vs. RBZ + laser: higher but not relevant VA

One study that compared RBZ alone or in combination with laser demonstrated a higher but not clinically relevant gain in mean visual acuity in the 'RBZ-only' group.

RBZ + prompt laser better than laser only

less improvement with RBZ + deferred laser

Finally, it has been evaluated whether RBZ in combination with prompt or deferred laser results in better outcomes than providing laser only. A significantly higher proportion (max. 30%) in the combined group with prompt laser gained ≥15 letters compared to the 'laser-only' group (max. 15 %). Additionally, the combined group achieved a higher improvement in vision related quality of life. The combination of RBZ with deferred laser demonstrated also better results than the 'laser-only' group, yet the improvement was lower than with prompt laser.

Pegaptanib

pegaptanib vs. sham: tendency for improvement but evidence unclear

The single study available demonstrates results in the direction of better visual acuity with intravitreal pegaptanib compared to sham injections, however differences were either not clinically relevant or of unknown significance. No evidence is available on improvement in vision related quality of life in pegaptanib trials.

Head-to-head comparisons

no head-to-head trials available

No evidence is available on the comparative effectiveness between the three products (head-to-head trial).

4.3 Safety

local events most common AE in all groups

mainly minor AE

According to the safety data in the studies (table 5-2), ocular events have been the most frequent adverse events stated. In up to 50% of eyes treated with bevacizumab, in up to 80% of the ranibizumab-treated eyes, in up to 53% of laser-treated eyes and in up to 70% in eyes with sham-injections ocular adverse events were registered. In 43% of patients who received ranibizumab plus laser, ocular adverse events were reported. However, most of the ocular adverse events are none-serious (e.g. eye pain, red eyes, transient increased intraocular pressure).

SAE: intraocular pressure, vitreous haemorrhage, endophtalmitis

Most frequent ocular serious adverse events stated were seriously increased intraocular pressure (<1% in bevacizumab; 5% in laser eyes; 8-16% in combined group of bevacizumab plus triamcinolone), vitreous haemorrhage (1% in ranibizumab-eyes; up to 9% in laser-treated eyes) and endophtalmitis (2% in ranibizumab-treated eyes; <1% in pegaptanib-treated eyes).

Additionally, studies reported systemic adverse events in one bevacizmab-study (4%), max. 60% in ranibizumab-treated and laser-treated patients, in 12% of patients post sham-injections and in 46% of patients who received ranibizumab plus laser. In some cases, relation to the treatment is very unlikely (e.g. metabolic events, cholecystectomy). Cardio-vascular events were reported in 7% of patients treated with ranibizumab and in 1%-4% of those treated with laser. 2% (2) of the patients in the ranibizumab-groups, 4% (2) of patients in the laser groups, 2% (1-2) of those in the ranibizumab + laser groups and 3% (1) of patients in the sham group died.

up to 60% systemic AE

cardio-vascular AE: max. 7% in anti-VEGF groups

relation to treatment often unclear

Overall proportions of serious adverse events reported ranged from 29% in patients treated with ranibizumab, 22% in those treated with laser to 15% in patients who received sham-injections.

total SAEs: 20% in RBZ, 22% in laser, 15% in sham-group

5 Quality of evidence

For assessing the quality of evidence we apply the concept by the GRADE working group [27]. GRADE uses the following classification and definitions for assessing the quality of the evidence:

quality of evidence according to GRADE

- High: further research is very unlikely to change our confidence in the estimate of effect
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimates
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very low: we are very uncertain about the estimate

Application of the GRADE-Scheme for our research question is presented in tables 5-1 and 5-2. Overall quality of evidence for the efficacy of anti-VEGF in the management of DME is moderate. Quality of evidence is higher for ranibizumab efficacy than for bevacizumab or pegaptanib efficacy. Quality of evidence for safety of any anti-VEGF product in the management of DME is very low.

efficacy: moderate quality of evidence; RBZ higher than IVB

safety: very low quality

Table 5-1: Evidence profile: efficacy of anti-VEGF versus comparators

No of studies/eyes/patients	Design	Limitations	Consistency of results	Directness	Effect size	Other modifying factors+	Quality of evidence
Outcome: mean change visual acuity (logMAR) Bevacizumab (IVB); between groups difference							
IVB/IVT:1/28/28	RCT	No ser. limit.	Only 1 trial	Some uncertainty#	-0.0117 better; not significant	Sparse data/low prec.	Low
IVB/IVT+IVB: 2/265/230	RCT	Ser. limit.##	Consistent	Direct	IVB+IVT -0.02 to -0.24 better; not significant	-	Moderate
IVB/MPC: 2/212/177	RCT	Ser. limit.±	No import. inconsist.	Some uncertainty#	-0.03 to -0.27 better; one study significant, one not	-	Low
IVB/MPC+IVB: 1/62/48	RCT	Ser. limit.±	Only 1 trial	Some uncertainty#	IVB+MPC: -0.07 better; not significant	-	Low
IVB/sham: 1/114/101	RCT	No ser. limit.	Only 1 trial	Some uncertainty	-0.21 better; significant, clinically relevant	-	Low
Outcome: mean change visual acuity (logMAR) Ranibizumab (RBZ) and Pegaptanib (PG); between groups difference							
Not measured							
Outcome: visual acuity (mean change ETDRS-letters) Bevacizumab (IVB); between groups difference							
IVB/MPC: 1/80/80	RCT	No limit.	Only 1 trial	Direct	+11.3 significant, clinically relevant	-	High
Outcome: visual acuity (mean change ETDRS-letters) Ranibizumab (RBZ); between groups difference							
RBZ/MPC: 2/471/471	RCT	Ser. limit.±±	Consistent	Direct	+6.2 to +6.8; significant, not clinic. relevant	-	Moderate
RBZ/MPC+RBZ: 1/126/126	RCT	Ser. limit. ¤¤	Only 1 trial	Direct	+3.4; not significant	-	Low
RBZ/sham: 1/151/151	RCT	No ser. limit.	Only 1 trial	Some uncertainty	+10.6 (h. dose) to +13.4 (l. dose); sign., clinic. relev.	-	Moderate
RBZ+MPC/MPC: 3/1325/1162	RCT	Ser. limit. ±±	consistent	Direct	+3.8 to +5.8; 2 sign., 1 not; not clinic. relevant	-	Moderate
RBZ+def. MPC/MPC: 1/854/691	RCT	Ser. limit.‡	Only 1 trial	Direct	+6; significant, not clinic. relevant	-	Moderate
Outcome: visual acuity (mean change ETDRS-letters) Pegaptanib (PG); between groups difference							
PG/sham: 1/172/172	RCT	Serious limit.‡‡	Only 1 trial	Direct	0.7 (high dose; not sign.) to 4.3 (sign.); not clinic. rel.	-	Moderate
Outcome: proportion of ≥15 ETDRS letters or ≥2 Snellen-lines gain Bevacizumab (IVB)							
IVB/IVT: 1/28/28	RCT	-			Not measured	-	-
IVB/IVT+IVB: 1/150/129	RCT	Ser. limit.##	Only 1 trial	Direct	Range: 31%-37%/21%-25%; significance unclear	-	Moderate
IVB/MPC: 2/230/209	RCT	Ser. limit.##	Consistent	Some uncertainty#	Range: 12%-37%/5%-15%; significance unclear	-	Low
IVB/MPC+IVB: 1/62/48	RCT	-			Not measured	-	-
IVB/sham: 1/115/101	RCT	-			Not measured	-	-
Outcome: proportion of ≥15 ETDRS letters or ≥3 Snellen-lines gain Ranibizumab (RBZ)							
RBZ/MPC: 2/471/471	RCT	Ser. limit.±±	Consistent	Direct	Range: 22%-23%/0%-8%; significant	-	Moderate
RBZ/MPC+RBZ: 1/126/126	RCT	Ser. limit. ¤¤	Only 1 trial	Direct	22%/8%; significance unclear	-	Low
RBZ/sham: 1/151/151	RCT	No ser. limit.	Only 1 trial	Some uncertainty	15% (higher dose) -18% (lower dose)/5%; significant	-	High
RBZ+MPC/MPC: 3/1325/1162	RCT	Ser. limit. ±±	Consistent	Direct	Range: 8% to 30%/0% to 15%; RR 2.09; significant	-	Moderate
RBZ+def. MPC/MPC: 1/854/691	RCT	Ser. limit.‡	Only 1 trial	Direct	28%/15%; RR 1.89; significant	-	Moderate
Outcome: proportion of ≥15 ETDRS letters or ≥3 Snellen-lines gain Pegaptanib (PG)							
PG/sham: 1/172/172	RCT	Serious limit.‡‡	Only 1 trial	Some uncertainty	7% (h. dose) -18% (l. dose) to 7% (sham); significance unclear	-	Moderate
Outcome: proportion of ≥15 ETDRS letters or ≥2 Snellen-lines loss Bevacizumab (IVB)							
IVB/IVT: 1/26/26	RCT	-			Not measured	-	-
IVB/IVT+IVB: 1/150/129	RCT	Ser. limit.##	Only 1 trial	Direct	Range: 0%-4%/15%-21%, not significant	-	Moderate
IVB/MPC: 2/230/209	RCT	Ser. limit.##	Consistent	Some uncertainty#	Range: 0%**-4%/5%**-23%; not significant	-	Low
IVB/MPC+IVB: 1/62/48	RCT	-			Not measured	-	-
IVB/sham: 1/115/101	RCT	-			Not measured	-	-

No of studies/eyes/patients	Design	Limitations	Consistency of results	Directness	Effect size	Other modifying factors+	Quality of evidence
Outcome: proportion of ≥15 ETDRS letters or ≥2 Snellen-lines loss Ranibizumab (RBZ)							
RBZ/MPC: 1/345/345	RCT	Ser. limit.¤	Only 1 trial	Direct	1%/8%; significance unknown	-	Low
RBZ/MPC+RBZ: 1/126/126	RCT	-			Not measured	-	-
RBZ/sham: 1/151/151	RCT	No ser. limit.	Only 1 trial	Some uncertainty	Range: 0%-3%/10%; significant	-	Moderate
RBZ+MPC/MPC: 2/1199/1036	RCT	Ser. limit.‡, ¤	Consistent	Direct	Range: 2% to 3%/8%; RR0.21; significant	-	Moderate
RBZ+def. MPC/MPC: 1/854/691	RCT	Ser. limit.‡	Only 1 trial	Direct	2%/8%; RR 0.28; significant	-	Moderate
Outcome: proportion of ≥15 ETDRS letters or ≥3 Snellen-lines gain or loss Pegaptanib (PG)							
Not measured							
Outcome: vision related quality of life (VFQ 25) Bevacizumab (IVB) and Pegaptanib (PG); between groups difference							
Not measured							
Outcome: vision related quality of life (VFQ 25) Ranibizumab (RBZ); between groups difference							
RBZ/MPC: 1/345/345	RCT	Ser. limit.¤	Only 1 trial	Direct	5.3; significant, clinic. relevant	-	Moderate
RBZ+MPC/MPC: 1/345/345	RCT	Ser. limit.¤	Only 1 trial	Direct	4.8; significant, clinic. relevant	-	Moderate

*clinic. relev.: clinically relevant; def. MPC: deferred laser photocoagulation; ETDRS: Early Treatment of Diabetic Retinopathy Study; h. dose: high dose; IVB: intravitreal bevacizumab; IVT: intravitreal triamcinolone; l. dose: low dose; limit.: limitations; logMAR: logarithm of the minimal angle of resolution; MPC: macular laser photocoagulation; n.a.: not applicable: no ser. limit.: no serious limitations; ser.: serious; sign.: significant; *low incidence, lack of precise data, sparse data, strong or very strong association, high risk of publication bias, dose-efficacy gradient, residual confounding plausible; **≥30 letters loss; #uncertain whether effect of single dose is sustained for 24 ws; ## allocation concealment unclear, incomplete outcome data not addressed, imbalance of baseline VA; ±sequence generation and allocation concealment unclear, blinding of outcome assessment unclear, incomplete outcome data not addressed, imbalance of disease severity at baseline; ±± allocation concealment unclear, no blinding of outcome assessment, incomplete outcome data not addressed; incomplete data; incomplete outcome data handled with 'last observation carried forward'; ¤ incomplete data; incomplete outcome data handled with 'last observation carried forward'; ‡ incomplete outcome data handled with 'last observation carried forward'; ‡‡ imbalance of baseline VA, incomplete outcome data; ¤¤ allocation concealment unclear, no blinding of outcome assessment, incomplete outcome data not addressed; incomplete data;*

Table 5-2: Evidence profile: safety of anti-VEGF and comparators

No of studies/eyes	Design	Limitations	Consistency of results	Directness	Effect size	Other modifying factors+	Quality of evidence
Outcome: adverse events bevacizumab							
6/218	RCT	Serious limit.#	Consistent	Direct	**Ocular:** any event: 19%-48%; transient chamber reaction: 2%-20%; IOP: 0.2%; PDR: 2%-8%; **Systemic:** 0%-4% **SAE:** IOP: 0.2%; Foot ulcer: 2%; cholecystectomy: 2%; no death	Very low incidence	Very low
Outcome: adverse events ranibizumab							
3/260	RCT	Serious limit.‡	Important inconsistencies	Direct	**Ocular:** Any: 40%-80%; VH: 1%; endophtalmitis: 2%; retinal ischaemia/artery occlusion: 1% **Systemic:** Any: 14%-58%; cardiac: 7%; metabolism: 2%-4%; vascular: 4%; infections: 2% **SAE:** Any: 29%; death: 2%(2); VH: 1%-2%; cardiac: 7%; metabol.: 2%-4%; vasc.: 4%; infect.: 2%; endophtalmitis: 2%; retinal ischaemia/artery occlusion: 1%	Very low incidence	Very low
Outcome: adverse events pegaptanib							
1/128	RCT	Serious limit.¤	Only 1 trial	Direct	**Ocular:** Endophtalmitis: 0.15% per injection; 0.8 per subject; any event: 85% **Systemic:** No systemic AE **SAE:** Endophtalmitis: 0.15% per injection; 0.8 per subject; any event: 16%	Very low incidence	Very low
Outcome: adverse events triamcinolone							
1/14	RCT	No serious limit.	Only 1 trial	Some uncert.	**Ocular:** Increase of IOP **Systemic:** No systemic AE **SAE:** No SAE	Very low incidence, sparse data	Very low
Outcome: adverse events laser photocoagulation							
5/555	RCT	Serious limit. #,‡	Consistent	Direct	**Ocular:** Any: 2%-53%; PDR: 3%-6%; neovasc.:3%; lens opacity: 2%; VH: 2%-9%; ocular vascular events: 0.4%; IOP:5% **Systemic:** Any: 4%-61%; fall: 3%; cardiac: 1%-4%; CVI: 3%; metabolism: 3%; vascular: 3%; infections: 3% **SAE:** Any: 2%-22%; VH: 3%-9%; death: 4%(2); ocular vascular events: 0.4%; IOP:5%; cardiac: 1%-4%; worsening angina: 3%; CVI: 3%; foot ulcer: 3%; metabolism: 3%; vascular: 3%; infections: 3%	Very low incidence	Very low
Outcome: adverse events sham injection							
3/127	RCT	Serious limit.¤	Some inconsistencies	Direct	**Ocular:** Any: 60%-70%; No injection related complication; retinal detachment: 2% **Systemic:** Any: 0%-12%; metabolism: 2%; vascular: 2%; infections: 3% **SAE:** Any: 15%; Death: 3% (1); IOP: 57%; retinal detachment: 2%; metabolism: 2%; vascular: 2%; infections: 3%	Very low incidence	Very low
Outcome: adverse events bevacizumab + triamcinolone							
2/87	RCT	Serious limit.±	Consistent	Direct	**Ocular:** IOP: 8%-16%; lens opacity: 0%-8%; VH:3%; PDR: 0%-8%; neovasc.: 8% **Systemic:** Not stated **SAE:** Death: 0% to 4% (2); VH: 1%; high risk PDR: 1%	Very low incidence	Vey low
Outcome: adverse events bevacizumab + photocoagulation							
1/22	RCT	Serious limit.##	Only 1 trial	Some uncert.	**Ocular:** No injection related complications **Systemic:** Not stated **SAE:** Not stated	Very low incidence, sparse data	Very low
Outcome: adverse events ranibizumab + laser							
2/348	RCT	Serious limit.‡‡	Consistent	Direct	**Ocular:** Any: 43%; VH: 2%; endophtalmitis: 0.5%; ocular vascular events: 0.2%; IOP: 4% **Systemic:** Any: 46%; cardiac: 0%-3%; metabolism: 2%; vascular: 1%-2%; infections: 3% **SAE:** Any: 2%-20%; VH: 2%; endophtalmitis: 0.5%; ocular vascular events: 0.2%; IOP: 4%; cardiac: 0%-3%; metabolism: 2%; vascular: 1%-2%; infections: 3%	Very low incidence	Very low

*AE: adverse event; CVI: cerebrovascular incidence; imp. inc.: important inconsistency; IOP: intraocular pressure; limit.: limitations; no imp. inc.: no important inconsistency; PDR: proliferative diabetic retinopathy; SAE: serious adverse event; uncert.: uncertainty; VH: vitreous haemorrhage; *low incidence, lack of precise data, sparse data, strong or very strong association, high risk of publication bias, dose-efficacy gradient, residual confounding plausible; #sequence generation and allocation concealment unclear, incomplete outcome data not addressed, blinding of outcome assessment unclear, imbalance of disease severity across groups at baseline; ‡allocation concealment unclear, no blinding of outcome assessment, incomplete outcome data not addressed; incomplete data; incomplete outcome data handled with 'last observation carried forward'; €imbalance baseline VA, incomplete outcome data; ±allocation concealment unclear, incomplete outcome data not addressed, imbalance of VA across groups at baseline; ##sequence generation and allocation concealment unclear, blinding of outcome assessment unclear, incomplete outcome data not addressed, imbalance of disease severity at baseline; ‡‡allocation concealment unclear, no blinding of outcome assessment, incomplete outcome data not addressed; incomplete data;*

6 Discussion

Current evidence has demonstrated that in a proportion of patients (on average 25%) VEGF-inhibitors result in better visual acuity than in patients treated with glucocorticoids or with laser photocoagulation. However, outcomes have been measured for a maximum of one year and the number of injections required for long-term improvement as well as general long-term efficacy is unknown.

more patients (¼) achieve improved VA than after alternative treatments

Even though anti-VEGF treatment has shown better outcomes than alternative treatments we need to be aware that in every study that analysed the proportion of patients who gained a clinically relevant number of letters/lines, the majority of patients (60% to 85%) did *not* achieve this improvement. Yet, this needs to be judged against the background that alternative therapies have primarily achieved stabilisation rather than improvement so far.

for small group progress because so far mainly stabilisation

Concerning the different products there is tentative evidence supporting the use of intravitreal bevacizumab injections in the treatment of DME, however quality of evidence is on average lower and follow-up is shorter in those studies than in the studies on ranibizumab. There is slightly stronger evidence supporting the use of intravitreal ranibizumab injections in the treatment of DME, yet, most of the 'ranibizumab-studies' have severe limitations, too. Concerning pegaptanib there is insufficient evidence to support its use in DME.

slightly stronger evidence for RBZ than IVB efficacy

Pegaptanib unclear

When comparing the products we need, however be aware that studies differed considerably concerning pre-entry treatment of the study population, number of doses and follow-up periods. Additionally, this limits transferability of study results into general practice.

different study designs make comparison difficult

Overall, high quality trials on bevacizumab included patients with refractory DME while in the ranibizumab trials inclusion was defined by the time period to prior treatment rather than by failure of prior treatment.

IVB-studies: patients with refractory DME, not so in RBZ-studies

In the bevacizumab studies patients mostly received a limited number of injections (some only one) while in the majority of ranibizumab trials the number of doses was unlimited. This may bias the results in favour of ranibizumab.

IVB-studies: limited number of injections,

bias towards RBZ

Follow-up was on average longer (1 year) in the ranibizumab trials than in the bevacizumab studies (6 months), hence 1-year benefits need yet to be demonstrated for bevacizumab. However, overall 1 year is a rather short time period for a chronic disease such as diabetic retinopathy and we still know little about long-term benefits or risks from this treatment.

longer follow-up in RBZ-trials

Concerning safety, the design of the studies and the number of patients is not suitable to detect rare adverse events. Hence, while neither study demonstrated serious safety problems, evidence is not sufficient to regard the products as safe in patients with DME. This relates to all three products analysed. Consequently, observational studies with a large number of patients and long-term follow-ups are needed. Large databases from age-related macular degeneration (AMD)-studies provide reassurance on the safety of intravitreal injections of ranibizumab [4] and bevacizumab [28, 29], however patient characteristics differ between those suffering from diabetic macular oedema and those with AMD.

safety: long-term observational studies required

economic issues: more patients can be treated with IVB due to large price difference

While off-label use of a product is definitely problematic, the 16-fold higher price per injection of ranibizumab compared to bevacizumab warrants health economic discussions. In a previous report [30] it was demonstrated that in a single clinic 1,800 more injections per year could be administered from the same resources available because bevacizumab was used in addition to ranibizumab instead of using the licensed product only. Vice versa, additional costs of 700.000 € would have occurred if ranibizumab only had been used. Hence, a much higher number of patients can be treated if bevacizumab is used.

NICE: RBZ not recommended for cost-effectiveness reasons

Our results are congruent with recent reviews [4, 6, 8, 31, 32]. Most importantly, while it was confirmed that ranibizumab is efficacious in the treatment of DME in a very recent NICE report, its use was not recommended for cost-effectiveness reasons [4].

many studies ongoing

Finally, many studies are currently ongoing. A recent NICE-review identified 22 studies on ranibizumab of which only one (non-industry-sponsored) compares ranibizumab against bevacizumab [4]. Furthermore there are eight ongoing trials on bevacizumab and five on pegaptanib. Re-evaluation at a later stage is highly recommended.

7 Conclusion

short-term efficacy of anti-VEGF for small group of patients

data don't suggest superiority of a single product, safety unclear

decision makers should take price differences and ongoing studies into account

Overall, for some patients with DME, VEGF-inhibitors seem to be a more effective short-term treatment than alternative therapies. Regardless of the registration status, the efficacy profile of anti-VEGF in patients with diabetic macular oedema is slightly in favour of ranibizumab, however, products have not been evaluated head-to-head so far and studies differ considerably concerning number of anti-VEGF doses and prior treatment. Hence, our evidence does not support superiority of one anti-VEGF over another. Concerning safety, the limited evidence available does not suggest serious safety problems in any of the products, yet the evidence is not of sufficient quality to confirm safety. Decision on financing should take into account the high price-difference between the products and the fact that many studies are still ongoing.

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9 Appendix: Search strategy

Medline via Ovid:

Database: Ovid MEDLINE(R) <1948 to January Week 2 2011>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 24, 2011>, Ovid MEDLINE(R) Daily Update <January 24, 2011>, Ovid OLDMEDLINE(R) <1946 to 1965>

Search Strategy:

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1 exp Diabetic Retinopathy/ (15692)

2 Diabetic Retinopathy.mp. (18713)

3 Diabetic macular oedema*.mp. (189)

4 Diabetic macular edema*.mp. (927)

5 *Macular Edema/ (2118)

6 (diabetic adj Macular Edema).mp. (925)

7 (diabetic adj Macular Oedema).mp. (189)

8 1 or 2 or 3 or 4 or 5 or 6 or 7 (19993)

9 Anti-VEGF*.mp. (1665)

10 Anti vascular endothelial growth factor*.mp. (471)

11 VEGF-inhibitor*.mp. (248)

12 Bevacizumab.mp. (4422)

13 Avastin.mp. (684)

14 Ranibizumab.mp. (681)

15 Lucentis.mp. (124)

16 Pegaptanib.mp. (360)

17 vascular endothelial growth factor inhibitor*.mp. (63)

18 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (6508)

19 8 and 18 (540)

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25.01.2011: Embase Session Results

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No. Query Results	Results	Date
#24. #8 AND #23	594	26 Jan 2011
#23. #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	4,372	26 Jan 2011
#22. 'vascular endothelial growth factor inhibitors'	51	26 Jan 2011
#21. 'vascular endothelial growth factor inhibitor'	37	26 Jan 2011
#20. 'pegaptanib'/exp/dd_vi	436	26 Jan 2011
#19. 'lucentis'/exp/dd_vi	661	26 Jan 2011

#18. 'ranibizumab'/exp/dd_vi	661	26 Jan 2011
#17. 'avastin'/exp/dd_vi	1,366	26 Jan 2011
#16. 'bevacizumab'/exp/dd_vi	1,366	26 Jan 2011
#15. 'vegf-inhibitors'	233	26 Jan 2011
#14. 'vegf-inhibitor'	145	26 Jan 2011
#13. 'vasculotropin inhibitor'/exp/dd_vi	127	26 Jan 2011
#12. 'anti vascular endothelial growth factors'	4	26 Jan 2011
#11. 'anti vascular endothelial growth factor'	529	26 Jan 2011
#10. 'anti vegfs'	7	26 Jan 2011
#9. 'anti vegf'	2,034	26 Jan 2011
#8. #1 OR #2 OR #3 OR #4 OR #5 OR #6	25,791	26 Jan 2011
#7. 'diabetic macular oedemas'		26 Jan 2011
#6. 'diabetic macular edemas'	3	26 Jan 2011
#5. 'diabetic macular edema'	1,590	26 Jan 2011
#4. 'diabetic macular oedema'	218	26 Jan 2011
#3. 'diabetic macular edema'/exp	942	26 Jan 2011
#2. 'diabetic retinopathy'	25,130	26 Jan 2011
#1. 'diabetic retinopathy'/exp	22,447	26 Jan 2011

.....

26.01.2011: CRD (DARE-NHS EED-HTA):

MeSH Diabetic Retinopathy EXPLODE 1 2 3
"Diabetic Retinopathy"
"Diabetic macular oedema"
"Diabetic macular edema"
MeSH Macular Edema EXPLODE 1
diabet* NEAR "Macular Oedema"
diabet* NEAR "Macular Edema"
#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
Anti-VEGF*
"Anti vascular endothelial growth factor"
"Anti vascular endothelial growth factors"
VEGF-inhibitor*
Bevacizumab
Avastin

Ranibizumab

Lucentis

Pegaptanib

"vascular endothelial growth factor inhibitor"

"vascular endothelial growth factor inhibitors"

#9 OR #10 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

#8 AND #20

13 Hits

The Cochrane Library:

Search Name: Anti-VEGF bei diabetischem Makulaödem

Comments: MEL 2011

Save Date: 2011-01-26 06:28:26.92

ID	Search
#1	MeSH descriptor Diabetic Retinopathy explode all trees
#2	"Diabetic Retinopathy"
#3	"Diabetic macular oedema"
#4	"Diabetic macular edema"
#5	MeSH descriptor Macular Edema explode all trees
#6	diabetic NEAR "Macular Edema"
#7	diabetic NEAR "Macular Oedema"
#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9	Anti-VEGF*
#10	"Anti vascular endothelial growth factor"
#11	"Anti vascular endothelial growth factors"
#12	VEGF-inhibitor*
#13	Bevacizumab
#14	Avastin
#15	Ranibizumab
#16	Lucentis
#17	Pegaptanib
#18	"vascular endothelial growth factor inhibitor"
#19	"vascular endothelial growth factor inhibitors"
#20	(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21	(#8 AND #20)

115 Hits