

Ranibizumab in Diabetic Macular Oedema – A Benefit–risk Analysis of Ranibizumab 0.5 mg PRN Versus Laser Treatment

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Introduction: The structured Benefit–risk Action Team (BRAT) approach aims to assist healthcare decision makers in treatment assessments. We applied BRAT to compare the benefit–risk profile of ranibizumab 0.5 mg versus laser photocoagulation for the treatment of diabetic macular oedema (DMO). **Methods:** One-year data for the ranibizumab 0.5 mg *pro re nata* (PRN) and laser arms of the phase III trials RESPOND (NCT01135914; n=220), RESTORE (NCT00687804; n=345), and REVEAL (NCT00989989; n=396) were included in the analysis. The benefit measures included ≥ 10 letters gain/avoidance of loss in best-corrected visual acuity (BCVA), achieving central retinal thickness (CRT) $< 275 \mu\text{m}$, and 25-item Visual Function Questionnaire (VFQ-25) outcomes. The risks measures included endophthalmitis, intraocular pressure increase, hypertension, proteinuria, arterial/venous thromboembolic events and deaths. **Results:** Ranibizumab treatment provided significant benefits compared with laser for ≥ 10 letter BCVA gain at month 12 (387/1,000 versus 152/1,000 patients), CRT $< 275 \mu\text{m}$ at 12 months (474/1,000 versus 348/1,000 patients), and improvement of ≥ 6.06 on the VFQ-25 near activities subscale (325/1,000 versus 245/1,000 patients). Results for the risk measures were similar for both treatments. **Conclusions:** Superior clinically relevant outcomes were observed with ranibizumab 0.5 mg PRN compared with laser without compromising on safety. This analysis further supports the positive benefit–risk profile of ranibizumab 0.5 mg PRN.

Keywords

Ranibizumab, laser, diabetic macular oedema, benefit–risk profile

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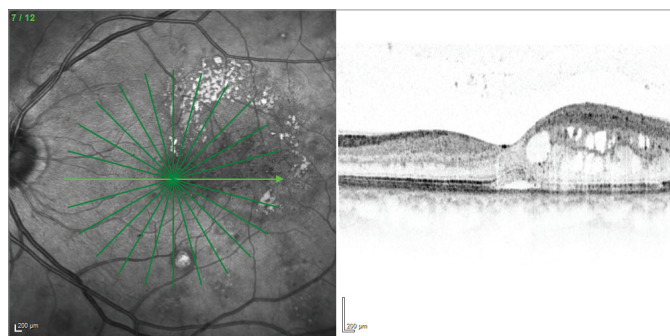
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Diabetic retinopathy is a common microvascular complication of diabetes, characterised by one or more features including retinal microaneurysms, cotton wool spots, microvascular abnormalities, hard exudates and haemorrhage, and, in the most severe form of the condition, neovascularisation.¹ Diabetic macular oedema (DMO) is a manifestation of diabetic retinopathy characterised by swelling of the macula due to a breakdown in the blood–retinal barrier, leading to hyperpermeability (*Figure 1*).² The retinal swelling caused by DMO is considered clinically significant if it involves or threatens the fovea, necessitating treatment to avoid potentially permanent vision loss.³ Central retinal thickness (CRT) can be measured using optical coherence tomography (OCT). OCT is a non-invasive imaging technique, and this parameter is often used alongside functional measures of vision (such as the number of letters that can be read from a vision chart) in order to monitor disease progression and response to therapy in patients with DMO. Without treatment, between a quarter and a third of eyes with clinically significant DMO will have significant vision loss within 3 years.⁴

In 1985, the Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated a net benefit of laser photocoagulation for the treatment of DMO,³ establishing laser as the gold standard for treatment at the time due to the technique's ability to stabilise vision in many patients, although improvements in visual function were uncommon.⁵ In a trial comparing laser with intravitreal triamcinolone acetate, treatment group differences at three years slightly favoured the laser group.⁶ However, laser treatment can cause atrophic changes in the retinal pigment epithelium (RPE), which may increase in size over time,⁷ thereby resulting in the formation of scotoma, a partial loss of vision or blind spot in an otherwise normal visual field.

Vascular endothelial growth factor (VEGF)-A plays a vital role within the vascular system as a regulator of developmental angiogenesis, vascular

Figure 1: Clinical presentation of diabetic macular oedema

Optical coherence tomography image presenting characteristic features of diabetic macular oedema.

permeability, and inflammation.⁸ However, elevated levels of VEGF-A within the eye have been implicated in the progression of hyperpermeability, and, therefore, in the evolution of DMO.⁹ Inhibition of VEGF-A, through the use of anti-VEGF treatments given as intravitreal injections, therefore provides an alternative strategy to laser photocoagulation. Ranibizumab, a humanised monoclonal antibody fragment, was the first such anti-VEGF treatment licensed for the treatment of DMO and is now approved for several retinal diseases.¹⁰ The binding of ranibizumab to active forms of VEGF-A prevents interaction of VEGF-A with its receptors on endothelial cells, thereby reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation. Ranibizumab treatment has been shown to lead to clinically significant improvements in visual acuity and has shown superiority on markers of visual acuity over laser therapy in a number of clinical trials.^{11–16} Since its introduction, anti-VEGF therapy has come to be considered by the majority of clinicians as first-line therapy for the treatment of DMO, with one survey of US retinal specialists reporting an increase in the use of anti-VEGF as the initial treatment for DMO from 25% in 2007 to over 60% in 2015.¹⁷

Owing to the crucial part that VEGF-A plays within the vascular system, the systemic safety of anti-VEGF therapies is an important consideration. When used systemically in an oncology setting, the anti-VEGF agent bevacizumab is associated with an increased risk of various vascular events.¹⁸ While the doses delivered to the eye for intravitreal use are much lower than those used to treat cancer, some anti-VEGF agents have been detected in the systemic circulation up to one month after intravitreal injection.¹⁹ Concerns that this systemic exposure may lead to an increase in vascular events, above that already anticipated in this higher-risk population, have been raised in a number of studies.^{20,21} The systemic exposure of an anti-VEGF agent is affected by its molecular structure; due to lack of the fragment crystallisable (Fc) portion of the parent antibody, the molecular structure of ranibizumab is small and it has low systemic exposure.¹⁹

In clinical practice, a range of different factors must be taken into account when making treatment decisions relating to patients with DMO, including reimbursement and/or insurance considerations, patient profile and situation (for example their history of comorbidities and whether they are retired or of working age), and the benefits and risks of the different therapeutic options must be balanced against each other. Therefore, in this analysis we report a structured benefit–risk analysis conducted using three controlled, clinical studies of ranibizumab 0.5 mg given according to a *pro re nata* (PRN) regimen versus laser treatment in patients with DMO. This analysis uses pooled patient-level data combined together across studies, which allows more in-depth analyses than the analysis of published study-level data typical of most published meta-

analyses. The results of this study are discussed within the context of other studies in DMO.

Methods

The Benefit–risk Action Team (BRAT) structured approach was developed by the Pharmaceutical Research and Manufacturers of America (PhRMA) BRAT, in order to present a structured framework to facilitate regulatory decision making.²² The BRAT framework enables the selection, organisation, summarisation and interpretation of data to provide a rationale for decision-making based on benefit–risk assessments.²² The structured benefit–risk analysis reported here was performed based upon the steps of this BRAT framework.

Selection of comparisons to be made

Ranibizumab 0.5 mg PRN was compared to laser photocoagulation as the previous gold standard therapy, with benefit and risk outcomes collated from trials which included a controlled period of 1 year (*Tables 1* and *2*).

Data to be included

Studies included in this analysis were limited to those pharmaceutical company-sponsored trials comparing a control laser arm with ranibizumab therapy from which the authors had full access to patient-level data, in order to provide the format laid out by BRAT, which is not available from published studies. Studies fulfilling the selection criteria were RESTORE (a phase III, multicentre, 12-month, double-masked, randomised study, predominantly [$>94\%$] Caucasian patients; $n=345$),¹³ REVEAL (a 12-month, phase III, multicentre, double-masked, randomised, laser-controlled study in Asian patients; $n=396$)¹⁴ and RESPOND (a 12-month, multicentre, open-label, parallel-group, randomised, active-controlled study, also predominately [87.7%] Caucasian patients; $n=220$).^{11,12} Additional published controlled studies of anti-VEGF therapy in DMO are included in the discussion section of this paper where relevant, but are not included in the pooled analysis for the following reasons:

- Studies where the authors did not have access to patient-level data and used anti-VEGF other than ranibizumab, for example DA VINCI, VIVID and VISTA.^{23,24}
- Studies in DMO that included a sham injection control arm rather than laser, for example RISE and RIDE.²⁵
- Studies in DMO with only active (anti-VEGF) control arms, for example Protocol T.²¹
- Single-arm studies in DMO with no control arm, for example RELIGHT.²⁶

Outcome measures

The outcome measures chosen by the authors for presentation in this structured benefit–risk analysis were selected from the predefined primary endpoints within the contributing studies, predefined patient-related outcomes, and the important safety topics included within the ranibizumab Risk Management Plan.²⁷ The selected endpoints were considered by the authors to be of high clinical relevance. In order to permit presentation of all selected endpoints on the same scale, a number of efficacy endpoints were transformed to a binary scale. For scores on the 25-item version of the National Eye Institute's Visual Function Questionnaire (VFQ-25), responsiveness thresholds were used.²⁸ The VFQ-25 can be divided into several subscales, each assessing a different aspect of visual function. In addition to the overall (composite) VFQ-25 score, three of the VFQ-25 subscales were included separately in the analysis as key aspects of vision-related quality of life for patients with DMO: near activities (e.g., reading), distance activities (e.g., ability to read street signs), and driving ability. The responsiveness threshold for the near activities subscale of the VFQ-25 was a change of 6.06. This was

Table 1: Key clinical trials of ranibizumab in patients with diabetic macular oedema

Study (reference)	ClinicalTrials.gov registration	Study design	Treatment (number of patients enrolled)
Studies comparing ranibizumab versus laser			
RESPOND ^{11,12}	NCT01135914	12-month, prospective, multicentre, randomised, open-label study using three parallel treatment arms	Ranibizumab 0.5 mg monotherapy (n=71); ranibizumab in combination with laser (n=70); laser monotherapy (n=62)
RESTORE ¹³	NCT00687804	12-month, randomised, double-masked, multicentre study	Ranibizumab 0.5 mg (n=116); ranibizumab in combination with laser (n=118); laser monotherapy (n=111)
REVEAL ¹⁴	NCT00989989	12-month, randomised, double-masked, multicentre, active-controlled study	Ranibizumab 0.5 mg monotherapy (n=133); ranibizumab in combination with laser (n=132); laser monotherapy (n=131)
Studies comparing ranibizumab versus sham			
RESOLVE ¹⁵	NCT00284050	Randomised, double-masked, multicentre, sham-controlled, phase II study	Ranibizumab 0.3 mg (n=51); ranibizumab 0.5 mg (n=51); sham (n=49)
RISE ^{16,25}	NCT00473382	Randomised, multicentre, double-masked, 3-year trial, sham-controlled phase III study	Ranibizumab 0.3 mg (n=125); ranibizumab 0.5 mg (n=127); sham (n=130)
RIDE ^{16,25}	NCT00473330	Randomised, multicentre, double-masked, 3-year trial, sham-controlled phase III study	Ranibizumab 0.3 mg (n=125); ranibizumab 0.5 mg (n=125); sham (n=127)
Other comparisons			
DRCR.net Protocol I ³³	NCT00445003	12-month, multicentre, randomised phase III study	Sham + prompt laser (n=293); ranibizumab + prompt laser (n=187); ranibizumab + deferred laser (n=188); triamcinolone + prompt laser (n=186)
DRCR.net Protocol S ³⁵	NCT01489189	2-year, multicentre, randomised, phase III study in patients with proliferative diabetic retinopathy	Pan retinal photocoagulation (n=203 eyes); ranibizumab 0.5 mg + deferred pan retinal photocoagulation (n=191 eyes)
DRCR.net Protocol T ²¹	NCT01627249	2-year, multicentre, randomised, phase III study	Aflibercept 2.0 mg (n=224); bevacizumab 1.25 mg (n=218); ranibizumab 0.3 mg (n=218)
RETAIN ³⁷	NCT01171976	2-year, single-masked, multicentre phase IIIb study	T&E regimen of ranibizumab with laser (n=121); treat-and-extend regimen of ranibizumab monotherapy (n=128); PRN regimen of ranibizumab monotherapy (n=123)

PRN = pro re nata; T&E = Treat and Extend.

chosen on the basis of it being a clinically relevant difference equivalent to a 15-letter gain in visual acuity in the study eye at 12 months in the MARINA pivotal phase III study of ranibizumab in neovascular age-related macular degeneration.²⁹

The selected benefits and risks presented in this benefit–risk analysis are (Figure 2):

- Benefits: gain of ≥ 10 letters in BCVA from baseline and avoidance of loss of ≥ 10 letters from baseline (well-recognised functional endpoints that provide a clinically meaningful measure); CRT $< 275 \mu\text{m}$ (an accepted anatomical limit of normal retinal size); patient-orientated VFQ-25 quality of life outcomes.
- Risks associated with intravitreal injection into the eye: endophthalmitis and the more general term of intraocular inflammation; intraocular pressure (IOP) increase.
- Risks known to be associated with systemic inhibition of VEGF: hypertension, proteinuria, myocardial infarction, non-myocardial arterial thromboembolic events (a composite endpoint that includes strokes, transient ischaemic attacks and arterial peripheral vascular events), venous thromboembolic events.
- Mortality endpoints: vascular and non-vascular deaths.

Adverse events were identified using pre-defined searches based upon appropriate Medical Dictionary for Regulatory Activities (MedDRA) hierarchy. Where possible, standard MedDRA queries were used.

The variables included in the structured benefit–risk assessment are included in a Forest plot output (Figure 2). The relative risk was expressed

as risk difference, which is always defined, including if the response or event rate is 0 in one or both treatment groups. Exact 95% confidence intervals (CI) were obtained by iterative computation.

Results

Benefit–risk analysis – efficacy outcomes

The selected endpoint of visual improvement showed increased benefits for ranibizumab versus laser (Table 3 and Figure 3). At month 12, the difference between ranibizumab and laser in the incidence rate of a gain from baseline in BCVA of ≥ 10 letters was significant, with an additional 235 subjects for every 1,000 treated achieving a gain from baseline in BCVA of ≥ 10 letters with ranibizumab (387 versus 152 per 1,000 patients for ranibizumab and laser, respectively; 95% CI 158.5, 310.2). There was a trend toward patients given ranibizumab being more likely to avoid a loss of 10 letters or more at 12 months (incidence rate of 969 versus 897 per 1,000 patients for ranibizumab and laser, respectively; 95% CI -5.8, 149.8). Furthermore, for every 1,000 patients, significantly more had a CRT of $< 275 \mu\text{m}$ at 12 months with ranibizumab than with laser (474 versus 348 per 1,000 patients, respectively; 95% CI 47.5, 202.2). Similar outcomes were seen for the comparisons between ranibizumab and laser on selected items of the quality of life VFQ-25 instrument, with a significant result on the rate of improvement on the near activities subscale by 6.06 or more at month 12 (325 versus 245 per 1,000 patients for ranibizumab and laser, respectively; 95% CI 1.7, 157.2).

Benefit–risk analysis – safety outcomes

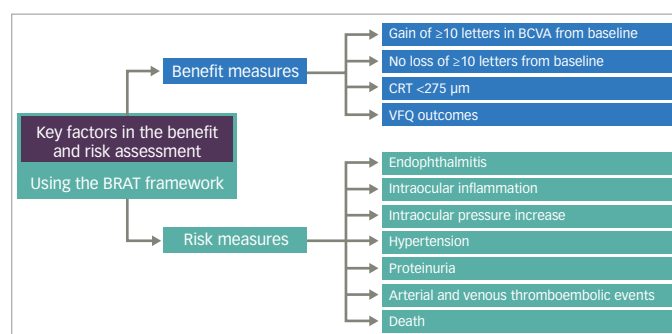
At month 12, there were no statistically significant differences observed in the rates of risk of selected ocular and systemic safety outcomes between ranibizumab 0.5 mg and laser treatment (Figure 3 and Tables 4

Table 2: Efficacy outcomes from key clinical trials

Studies comparing ranibizumab versus laser				
Study	Characteristics	Ranibizumab 0.5 mg + laser	Ranibizumab 0.5 mg	Laser
RESPOND ^{11,12†}	Mean BCVA gain, ETDRS letters	+8.2	+8.9	+0.3
	BCVA gain of ≥10 ETDRS letters	34.4%	52.1%	16.1%
	Avoided BCVA loss of ≥10 ETDRS letters	–	–	–
	Mean CRT change, µm	–152.2	–143.5	–107.1
RESTORE ^{13†}	Mean BCVA gain, ETDRS letters	+5.9	+6.1	+0.8
	BCVA gain of ≥10 ETDRS letters	43.2%	37.4%	15.5%
	Avoided BCVA loss of ≥10 ETDRS letters	95.8%	96.5%	87.3%
	Mean CRT change, µm	–118.7	–128.3	–61.3
REVEAL ^{14†}	Mean BCVA gain, ETDRS letters	+6.4	+6.8	+1.8
	BCVA gain of ≥10 ETDRS letters	37.2%	33.8%	13.3%
	Avoided BCVA loss of ≥10 ETDRS letters	94.6%	97.0%	93.8%
	Mean CRT change, µm	–163.8	–148.0	–57.1
Studies comparing ranibizumab versus sham				
Study	Characteristics	Ranibizumab 0.5 mg	Sham	
RESOLVE ^{15†}	Mean BCVA gain, ETDRS letters	+10.3	–1.4	
	BCVA gain of ≥10 ETDRS letters	60.8%	18.4%	
	Avoided BCVA loss of ≥10 ETDRS letters	95.1%	75.5%	
	Mean CRT change, µm	–194.2	–48.4	
RISE ^{16*}	Mean BCVA gain, ETDRS letters	+12.5	+2.6	
	BCVA gain of ≥10 ETDRS letters	62.4%	29.9%	
	Avoided BCVA loss of ≥10 ETDRS letters	–	–	
	Mean CFT change, µm	–253.1	–133.4	
RIDE ^{16*}	Mean BCVA gain, ETDRS letters	+12.0	+2.3	
	BCVA gain of ≥10 ETDRS letters	64.4%	25.4%	
	Avoided BCVA loss of ≥10 ETDRS letters	–	–	
	Mean CFT change, µm	–270.7	–125.8	

†Data for Month 12; *Data for Month 24; BCVA = best-corrected visual acuity; CFT = central foveal thickness; CI = confidence interval; CRT = central retinal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study.

Figure 2: Decision tree for the use of ranibizumab in patients with diabetic macular oedema



BCVA = best-corrected visual acuity; BRAT = benefit-risk action team; CRT = central retinal thickness; VFQ = Visual Functional Questionnaire.

and 5). Raised IOP was reported as an adverse event with ranibizumab treatment but not with laser (46 versus 0 per 1,000 patients, respectively; 95% CI -31.5, 124.2).

The number of events of endophthalmitis and intraocular inflammation in ranibizumab-treated patients was low (1 and 3 in a total of 323 patients, respectively; Table 4). Hypertension was the most common systemic adverse event reported in both ranibizumab and laser groups

(68 versus 71 per 1,000 patients, respectively; 95% CI –80.4, 75.4). Rates of all other systemic adverse events assessed (proteinuria, myocardial infarction, non-myocardial arterial thromboembolic events [including strokes, transient ischemic attacks and arterial peripheral vascular events], venous thromboembolic events, vascular and non-vascular deaths) were extremely low and balanced between ranibizumab and laser-treated patients – between 3 and 19 events per 1,000 patients for ranibizumab and between 3 and 22 events per 1,000 patients for laser (Table 5).

Treatment exposure

The mean number of ranibizumab 0.5 mg injections administered in the patients from the ranibizumab 0.5 mg monotherapy group was 7.0 to 9.2. The mean number of laser treatments received by patients in the laser monotherapy group ranged from 1.9 to 2.6.

Discussion
Benefit–risk analysis of ranibizumab 0.5 mg versus laser

This benefit–risk analysis pooled data from three phase III clinical studies of ranibizumab in DMO^{11–14} in a patient-level data meta-analysis that utilised the BRAT framework to select for analysis those efficacy and safety endpoints which the authors considered important for clinical decision making (Figure 2). Based upon the identified endpoints, the

Table 3: Benefit–risk analysis – efficacy outcomes

Benefit measures at month 12	Ranibizumab 0.5 mg PRN (n=323)		Laser (n=310)		Difference in incidence rate per 1,000 patients, ranibizumab 0.5 mg PRN versus laser (95% CI)
	Number of patients	Incidence rate per 1,000 patients	Number of patients	Incidence rate per 1,000 patients	
Gain of ≥10 letters in BCVA from baseline at month 12	125	387	47	152	235 (158.5, 310.2)
Without loss of ≥10 letters in BCVA from baseline at month 12	313	969	278	897	72 (–5.8, 149.8)
CRT <275 µm at month 12	153	474	108	348	125 (47.5, 202.2)
VFQ-25: near-activities subscale improved by ≥6.06 at month 12	105	325	76	245	80 (1.7, 157.2)
VFQ-25: distance activities subscale improved by ≥5.38 at month 12	89	276	68	219	56 (–21.8, 133.9)
VFQ-25: patients who could drive at month 12	122	378	108	348	29 (–48.8, 107.1)

Discrepancies in language translation in one country have been identified since the original RESTORE analysis; therefore, mental health dependency related VFQ questions 20–25 were excluded for RESTORE. BCVA = best-corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; PRN = pro re nata; VFQ = Visual Functional Questionnaire.

analysis supports the superior efficacy of ranibizumab 0.5 mg versus laser and demonstrates a similar safety profile of the two treatments, giving ranibizumab 0.5 mg a superior benefit–risk profile relative to laser therapy in the treatment of patients with DMO.

For the benefits analysed, significant differences were observed in favour of ranibizumab 0.5 mg PRN treatment at month 12 in three key areas: overall visual function, measured as the ability to read an additional 2 lines (gain of ≥10 letters in BCVA from baseline) on an ETDRS vision chart; anatomical improvement in terms of reduction of the thickness of the macular oedema (measured by the number of patients who achieved a CRT <275 µm); and quality of life as measured using patient-reported outcomes scales (improvement on the VFQ-25 near activities subscale by ≥6.06).

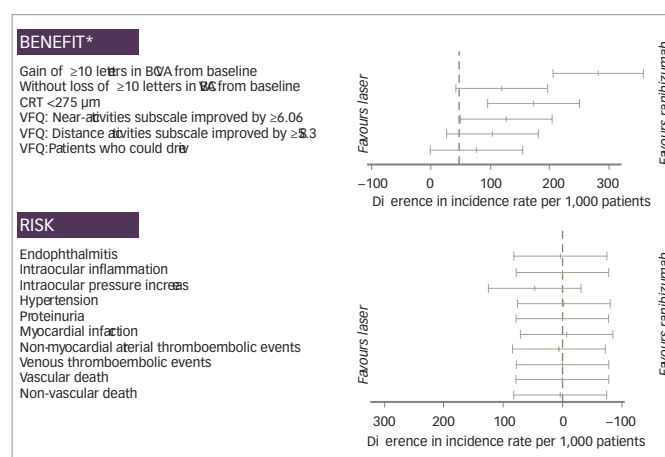
There are two elements that should be considered when assessing these efficacy gains with anti-VEGF therapy compared with laser: improvements due to inhibition of neovascularisation and oedema associated with DMO, and the reduction in focal scarring that is associated with focal laser.

When the retina is treated with laser, a decrease in retinal sensitivity related to laser coagulation spots is seen, and there is the potential for lesions to enlarge over time to involve the fovea.^{30,31} The non-destructive nature of treatment with ranibizumab appears in accordance with the lower rate of visual loss (≥10 letters) seen with ranibizumab in the studies pooled for this analysis and the reduced reading speed seen in some patients treated with laser photocoagulation, reported elsewhere.³²

Potential additional benefits of ranibizumab treatment

Intravitreal ranibizumab 0.5 mg was compared with laser/grid laser alone for the treatment of DMO in the Protocol I trial carried out by the Diabetic Retinopathy Clinical Research Network (DRCR.net).³³ Diabetic retinopathy progression from baseline to the 1-year primary outcome visit was less likely to occur in eyes treated with ranibizumab compared with those given sham plus prompt laser. Similarly, in the RISE and RIDE trials, significantly more patients treated with ranibizumab 0.5 mg versus sham achieved a two- or three-step improvement on the ETDRS diabetic retinopathy severity scale (a scoring system which classifies the stages of the disease) at month 24 (35.9% versus 5.4% for a two-step improvement, and 14.5% versus 1.3% for a three-step improvement for ranibizumab and laser, respectively, both $p < 0.001$).³⁴ Since the additional benefits of ranibizumab over laser are seen not only on DMO but also on diabetic retinopathy disease progression, these findings suggest that ranibizumab may have a disease modifying effect on the underlying diabetic retinopathy pathology. Indeed, the Protocol S trial, also carried out by the DRCR.net, has recently reported statistically significantly

Figure 3: Forest plot of efficacy and safety endpoints of ranibizumab versus laser treatment in patients with diabetic macular oedema



*At month 12; BCVA = best-corrected visual acuity; CRT = central retinal thickness; M = month; VFQ = Visual Functional Questionnaire.

greater gains in visual acuity over 2 years with ranibizumab versus pan-retinal photocoagulation (PRP; the application of many small laser spots across the retina but avoiding the central area) in patients with proliferative diabetic retinopathy (PDR; 2.8 versus 0.2 letters, $p < 0.001$), with ranibizumab remaining more effective than PRP in the treatment of PDR, even in patients without DMO.³⁵

The current EU label for ranibizumab allows for a flexible, individualised treatment approach with monitoring and treatment intervals based on disease activity, which enables physicians to choose a treatment schedule with reduced visit burden.^{36,37} This flexibility of dosing is particularly valuable in the management of patients with DMO, as long-term clinical trial evidence shows that the number of treatments required to maintain visual gains from anti-VEGF therapy reduces markedly over time, from 8–9 injections in the first year of treatment, to 0–1 injections in years 4 and 5.³⁸

Ophthalmic risks of ranibizumab

Endophthalmitis is a severe inflammation of the anterior and/or posterior chambers of the eye and is a potential risk following any intravitreal injection into the eye. It may be sterile or associated with bacterial infection (e.g., *staphylococci* or *streptococci*), with the risk minimised through proper injection technique and aseptic procedure. Patients must be made aware of the potential for endophthalmitis, to allow

Table 4: Benefit–risk analysis – ocular safety outcomes

Risk measures at month 12	Ranibizumab 0.5 mg PRN (n=323)		Laser (n=312)		Difference in incidence rate per 1,000 patients, ranibizumab 0.5 mg PRN versus laser (95% CI)
	Number of patients with at least one event	Incidence rate* per 1,000 patients	Number of patients with at least one event	Incidence rate* per 1,000 patients	
Endophthalmitis	1	3	0	0	3 (-74.9, 81.1)
Intraocular inflammation including uveitis	3	9	3	10	0 (-78.2, 77.7)
Retinal detachment, retinal tear and RPE tears	0	0	0	0	0
Intraocular pressure increase	15	46	0	0	46 (-31.5, 124.2)

*Incidence rate of patients with one or more relevant events per 1,000 patients. CI = confidence interval; PRN = pro re nata; RPE = retinal pigment epithelium.

Table 5: Benefit–risk analysis – systemic safety outcomes

Risk measures at month 12	Ranibizumab 0.5 mg PRN (n=323)		Laser (n=312)		Difference in incidence rate per 1,000 patients, ranibizumab 0.5 mg PRN versus laser (95% CI)
	Number of events	Incidence rate per 1,000 patients	Number of events	Incidence rate per 1,000 patients	
Hypertension	22	68	22	71	-2 (-80.4, 75.4)
Proteinuria	2	6	2	6	0 (-78.2, 77.8)
Myocardial infarction	5	15	7	22	-7 (-84.7, 71.2)
Non-myocardial arterial thromboembolic events	6	19	4	13	6 (-72.1, 83.8)
Venous thromboembolic events	2	6	2	6	0 (-78.2, 77.8)
Vascular death	1	3	1	3	0 (-78.1, 77.9)
Non-vascular death	2	6	1	3	3 (-75.0, 81.0)

CI = confidence interval; PRN = pro re nata.

timely assessment, diagnosis and treatment. Rates of endophthalmitis following intravitreal injection are extremely low, with only one instance of endophthalmitis (in a patient given ranibizumab) reported across the three studies included in this analysis (Table 4). Outside the studies included in this analysis, the rate of endophthalmitis over 3 years in the RISE and RIDE studies was 1.2%, or around 0.06% per injection,²⁵ the rate over two years in Protocol T was 0.45%, evenly split across all treatment arms,²¹ while no cases of endophthalmitis were observed over 100 weeks in the VIVID and VISTA studies.²⁴ In the LUMINOUS 30,000-patient, real-world evidence observational study, the overall rate of endophthalmitis was three events in 4,710 patients with DMO (0.06%) or three cases in 19,258 injections (0.016%).³⁹

Transient increases in IOP have been seen within 60 minutes of injection of ranibizumab.⁴⁰ In this analysis, IOP was reported as an adverse event in 4.6% of subjects receiving ranibizumab and in no patients receiving laser. Following the administration of intravitreal injections, IOP and the perfusion of the optic nerve head must be checked.

Systemic risks of ranibizumab

VEGF plays a crucial role within the cardiovascular system as a regulator of normal and pathological angiogenesis, vascular permeability and inflammation. Systemic VEGF inhibition using intravenous bevacizumab for the management of colon cancer has been associated with hypertension, thrombo-embolism (arterial and venous), haemorrhage, congestive heart failure, cardiac arrhythmia, proteinuria, gastro-intestinal perforation, surgery and wound healing complications.¹⁸ For the treatment of DMO, anti-VEGF therapy is administered as an intravitreal injection in order to deliver effective drug concentrations to the retina while minimising any systemic exposure. Only a fraction of the administered dose of ranibizumab reaches the systemic circulation, and even then it has a very short half-life (around 2 hours),

as a result of the molecule’s small size and lack of the Fc portion of the antibody,⁴⁰ giving it a low systemic exposure.⁴¹ Even so, it is important to be mindful of any potential risk associated with even low levels of exposure when considering the large DMO patient population receiving intravitreal anti-VEGF in clinical practice, and the high risk of systemic comorbidities including cardiovascular and cerebrovascular events in patients with DMO.⁴²

The comparison of systemic risks between ranibizumab and laser across the three trials included in this analysis does not show significant differences in systemic safety between subjects receiving ranibizumab and those randomised to laser. Both myocardial arterial thrombotic events (ATEs) and non-myocardial ATEs (a collection of adverse events that include strokes, transient ischemic attacks and peripheral vascular events) were reported at similarly low rates in both ranibizumab and laser-treated subjects, with no overall excess compared with laser treatment over the 1 year of observation in these trials.

Additional meta-analyses have been conducted to pool data from controlled studies in which ranibizumab was compared with sham or laser treatment. In a meta-analysis of six controlled phase II and III clinical trials conducted by Novartis and Genentech (1,767 patients in total, 936 treated with ranibizumab 0.5 mg [1095 patient-years]), no meaningful differences in cardiovascular or cerebrovascular safety were observed for ranibizumab 0.5 mg compared with sham and laser control participants (Table 6).⁴³ In another recent pooled analysis, Avery and colleagues have published data from four pivotal registration trials for Lucentis (RISE/RIDE) and Eylea (VISTA/VIVID).²⁰ These trials were sham injection controlled and required monthly dosing. Avery et al. have reported an increase in stroke, but not myocardial infarction, with both agents, and concluded that caution may be required when using these agents in the subgroup of what was described as ‘high risk patients’

Table 6: Pairwise cardiovascular and cerebrovascular safety comparisons for ranibizumab 0.5 mg versus control and ranibizumab 0.3 mg versus control from a pooled analysis of six phase II and III clinical trials (n=1,767)⁴³

Adverse event	Ranibizumab 0.5 mg versus control		Ranibizumab 0.3 mg versus control	
	Ranibizumab 0.5 mg, rate per 100 patient-years (n/N)	Control, rate per 100 patient-years (n/N)	Ranibizumab 0.3 mg, rate per 100 patient-years (n/N)	Control, rate per 100 patient-years (n/N)
Stroke plus transient ischemic attack	1.38 (15/936)	1.76 (13/581)	1.29 (6/250)	2.43 (11/251)
Stroke excluding transient ischemic attack	1.29 (14/936)	0.94 (7/581)	0.64 (3/250)	1.09 (5/251)
Myocardial infarction	1.47 (16/936)	2.02 (15/581)	2.62 (12/250)	2.87 (13/251)
APTC events	2.96 (32/936)	3.12 (23/581)	3.72 (17/250)	3.78 (17/251)
Vascular deaths	0.73 (8/936)	0.40 (3/581)	1.07 (5/250)	0.43 (2/251)

APTC = Antiplatelet Trialists Collaboration.

requiring monthly injections.²⁰ Clinical studies that compare the safety of the available anti-VEGF agents within the same study are limited.

The 2-year analysis of Protocol T reported an increased rate of Anti-Platelet Trialists' Collaboration (APTC) events in ranibizumab 0.3 mg-treated patients compared with those receiving bevacizumab or aflibercept; albeit, not statistically different from that of patients treated with the other anti-VEGF agents after adjusting for baseline risk factors.²¹ The authors noted the variability of their safety results compared with those consistently reported in previous clinical trials of ranibizumab 0.5 mg in DMO, and stated that the 'inconsistencies in the totality of the evidence create uncertainty as to whether there is a true increased risk of APTC events with ranibizumab at this time'.²¹

Strengths and weaknesses of this analysis

The strengths of this analysis include the fact that it pools together patient-level data from three randomised, controlled, phase III trials, and presents in a single graphical format the key benefits and risks of the two treatment options considered.

In terms of weaknesses, this analysis does not include any of the other available treatment options for DMO (including other anti-VEGF agents or steroids), as the authors did not have access to patient-level data for any trials fitting the inclusion criteria, other than those sponsored by Novartis. This analysis includes only the dose of ranibizumab approved within Europe (0.5 mg) – the studies meeting the inclusion criteria for this analysis did not include the 0.3 mg dose approved for use in

DMO and diabetic retinopathy for monthly use in the US. It was also not possible to include in this analysis a number of endpoints that may have proved important, including measures of retinal scarring (as scarring was not specifically defined or scored within the selected trials) and focal loss of vision (again, as this was not specifically tested within the trials). The analysis did not take into consideration any effect of injection frequency on level of systemic risk. The patient-level data included in our analysis may not be an accurate reflection of the general DMO population as a result of clinical trial exclusion criteria selecting against those at highest risk of systemic cardio- and cerebrovascular events. Finally, this analysis, like many other clinical trials and meta-analyses, lacks sufficient power to detect differences in absolute risk rates for rare safety events such as arterial thromboembolic events and vascular death. It might be that the risk–benefit profile is different for subgroups of individual patients.

In this benefit–risk analysis comparing ranibizumab 0.5 mg PRN with laser treatment, significant benefits were seen with ranibizumab 0.5 mg PRN over laser therapy, on benefit measures including gain of ≥ 10 letters in BCVA from baseline, achievement of CRT $< 275 \mu\text{m}$, and patient-reported quality of life outcomes. There were no clinically relevant differences in key ocular and systemic safety endpoints. The authors consider that the BRAT framework, facilitating the summary of key efficacy and safety endpoints into a single chart, may help when counselling patients with regard to the specific benefits and risks of the laser and ranibizumab therapy approaches. Consultation and decision should be made on the basis of the individual scenario including adherence and reimbursement. □

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