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Comparative efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion: a network meta-analysis

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ABSTRACT

Objective: To compare the efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion (BRVO).

Design: Randomised controlled trials (RCTs) evaluating the efficacy and safety of approved treatments for macular oedema secondary to BRVO were identified from an updated systematic review.

Setting: A Bayesian network meta-analysis of RCTs of treatments for macular oedema secondary to BRVO.

Interventions: Ranibizumab 0.5 mg pro re nata, aflibercept 2 mg monthly (2q4), dexamethasone 0.7 mg implant, laser photocoagulation, ranibizumab +laser, or sham intervention. Bevacizumab and triamcinolone were excluded.

Outcome measures: Efficacy outcomes were mean change in best corrected visual acuity (Early Treatment Diabetic Retinopathy Study scale) and the percentage of patients gaining ≥15 letters. Safety outcome was the percentage of patients with increased intraocular pressure (IOP)/ocular hypertension (OH).

Results: 8 RCTs were identified for inclusion with 1743 adult patients. The probability of being the most efficacious treatment at month 6 or 12 based on letters gained was 54% for ranibizumab monotherapy, 30% for aflibercept, 16% for ranibizumab plus laser (adjunctive or prompt), and 0% for dexamethasone implant, laser or sham. The probability of being the most efficacious treatment for patients gaining ≥15 letters was 39% for aflibercept, 35% for ranibizumab monotherapy, 24% for ranibizumab plus laser, 2% for dexamethasone implant, and less than 1% for laser or sham. There was no statistical difference between ranibizumab monotherapy and aflibercept for letters gained (+1.4 letters for ranibizumab vs aflibercept with 95% credible interval (CrI) of −5.2 to +8.5 letters) or the OR for gaining ≥15 letters: 1.06 (95% CrI 0.16 to 8.94)). Dexamethasone implant was associated with significantly higher IOP/OH than antivascular endothelial growth factor agents (OR 13.1 (95% CrI 1.7 to 116.9)).

Conclusions: There was no statistically significant difference between ranibizumab and aflibercept.

Strengths and limitations of this study

- Randomised controlled trials (RCTs) evaluating the efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion (BRVO) were identified from a published systematic review and database searches.
- Inclusion/exclusion criteria for the key variables baseline BCVA and duration of disease were matched in the RCTs evaluating antivascular endothelial growth factor (VEGF) therapy.
- Despite matching for baseline best corrected visual acuity (BCVA) and duration of disease, substantial heterogeneity existed between anti-VEGF RCTs.
- Two clinical trials included in the meta-analysis were unpublished, and therefore their quality could not be assessed.
- For one study, the SE for letters gained was graphically estimated. For another study, the SD was assumed.

INTRODUCTION

Branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) are important causes of visual impairment, and are thought to be the result of thrombotic events, external compression, or vessel wall pathology.[1–3] Occlusion of the major veins of the retinal circulation leads to increased intraluminal pressure, haemorrhage and oedema. Macular oedema secondary to RVO (BRVO or CRVO) is the second most common retinal vascular disease after diabetic retinopathy.[4 5]

The treatment of choice for patients with macular oedema associated with BRVO has long been considered to be grid laser photocoagulation.[6–8] However, the recent introduction of pharmacotherapies specifically targeting vascular endothelial growth factor (VEGF), such as ranibizumab and aflibercept,

has widened the range of therapeutic options. The efficacy of ranibizumab, a monoclonal anti-VEGF antibody fragment, in the treatment of BRVO was demonstrated in the Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO) phase 3 trial.[9] Following publication of these results, ranibizumab was approved in the USA[10] and EU[11] for the treatment of macular oedema secondary to RVO. The efficacy of aflibercept, an anti-VEGF binding protein, was demonstrated in the VIBRANT phase 3 trial,[12] and aflibercept has been submitted for approval in macular oedema secondary to BRVO in the EU.[13] An intravitreal dexamethasone implant is approved for patients with macular oedema secondary to RVO.[14][15] Other therapies include triamcinolone, a corticosteroid with a mechanism of action similar to dexamethasone, which is used off-label in this treatment setting;[16–18] and bevacizumab, an anti-VEGF agent, which is not licensed for the treatment of visual impairment of any aetiology. Thus, triamcinolone and bevacizumab were both excluded from the current analysis.

Given the number of treatments that have been developed for RVO, there is a need for an evidence-based analysis of the comparative efficacy of the different treatments available. With this in mind, Glanville *et al*[19] recently published a systematic review of randomised controlled trials (RCTs) evaluating the efficacy and safety of widely used treatments for macular oedema secondary to RVO. The main findings were that both ranibizumab and dexamethasone implants produced significantly greater improvements in best corrected visual acuity (BCVA) at 6 months in patients with RVO, when compared with individuals receiving sham intervention.

The current analysis adds to the Glanville *et al*[19] study by conducting a Bayesian network meta-analysis of all relevant RCTs, with the aim of comparing the efficacy and safety of all currently approved treatments or treatments submitted for approval for macular oedema secondary to RVO, comprising ranibizumab 0.5 mg, aflibercept 2 mg, dexamethasone 0.7 mg implant and laser photocoagulation.

METHODS
Glanville *et al* study
In brief, this was a systematic review of RCTs reporting the efficacy and safety of available treatments for macular oedema secondary to RVO.[19] The literature search was performed on 18 November 2010 using the databases Medline (including Medline In-Process), EMBASE, the Cochrane Library and Cumulative Index to Nursing and Allied Health Literature. Additional searches were performed in the ClinicalTrials.gov registry and the Association for Research in Vision and Ophthalmology (ARVO) database. The interventions included in the searches were ranibizumab, bevacizumab, dexamethasone and laser photocoagulation (bevacizumab was not included in our analysis). Primary efficacy outcomes were mean change in BCVA from baseline to month 6 (assessed

in terms of Early Treatment Diabetic Retinopathy Study (ETDRS) letters) and the number of patients gaining at least 10 letters from baseline to month 6. To be included, studies had to be RCTs that reported at least one primary efficacy outcome. The number of patients gaining at least 15 letters were also reported if available. In addition, RCTs had to comprise at least two treatment arms, including one active comparator of interest. Only RCTs in English were considered.

Updated search strategy
An updated search of Medline (including Medline In-Process), EMBASE and the Cochrane Library, using the search terms described in the study by Glanville *et al* (see online supplementary materials), was performed on 4 August 2014 to identify relevant RCTs that had been published since November 2010 (the date of the earlier study). Studies published in English, French and German were considered eligible for inclusion in the review.

Inclusion/exclusion criteria for the network meta-analysis
To be included in the current analysis RCTs had to meet the following criteria: (1) report at least one efficacy outcome of interest (mean change in BCVA from baseline or percentage of patients gaining ≥15 letters from baseline); (2) the outcome of interest had to be measured at 6 or 12 months from study baseline, with 6-month data used for the analysis when available; (3) have at least two interventions of interest, including sham injections, ranibizumab 0.5 mg monthly or pro re nata (PRN; as needed), aflibercept 2 mg monthly (2q4), dexamethasone 0.7 mg implant (retreatment interval ≥6 months) and prompt laser photocoagulation therapy; (4) patients receiving anti-VEGF had a PRN or monthly regimen. RCTs in which efficacy data for BRVO and CRVO were not presented separately were excluded.

Data sources and extraction
RCTs evaluating the efficacy and safety of treatment for macular oedema secondary to RVO were identified from three main sources: (1) the study by Glanville *et al*;[19] (2) the updated search strategy described above and (3) manual searches of the ClinicalTrials.gov registry, proprietary data on file at Novartis Pharma AG, and abstracts from ophthalmology congresses, including ARVO, American Academy of Ophthalmology (AAO) and European Society of Retina Specialists (EURETINA) congresses. To the best of our knowledge, there were no additional relevant proprietary data on file at Genentech.

Study characteristics, including baseline characteristics, number of patients, country and key inclusion/exclusion criteria, and study quality, were captured in Microsoft Excel spreadsheets.

Study quality assessment
The quality of each RCT was assessed according to the methodology checklist detailed in Appendix C of the National Institute for Health and Care Excellence

Guidelines Manual 2012.[20] In brief, these guidelines allow for assessment of the likelihood of bias in selection (systematic differences between comparator groups), attrition (systematic differences between comparator groups with respect to loss of participants), detection (systematic differences in how outcomes are ascertained, diagnosed or verified) and performance (systematic differences between comparator groups in the care provided, other than in the intervention under investigation).

Network meta-analysis

A Bayesian network meta-analysis with random treatment effects was used to compare mean change in BCVA from baseline to month 6, OR for gaining at least 15 letters, and OR for an increase in intraocular pressure (IOP)/ocular hypertension (OH) across the RCTs. The model did not converge when we consider IOP/OH rates separately for ranibizumab and aflibercept. As the rates of increased IOP/OH were small and comparable for ranibizumab (0–5%) and aflibercept (2%), rates of increased IOP/OH for ranibizumab and aflibercept were pooled to give an anti-VEGF rate of increased IOP/OH. This assumption is discussed in the Results section.

To estimate the posterior distribution for each model, two Markov chain Monte Carlo simulations were initialised using 27 000 iterations for each simulation. However, results are reported after excluding the first 2000 iterations (ie, results are reported for 25 000 iterations per chain). A 95% CrI was created using the 2.5 and 97.5 centiles of the posterior distribution. The overall relative treatment effect was calculated using the median value from the posterior distribution. A relative treatment effect was interpreted as significant if the 95% CrI for the OR did not include 0 or if the 95% CrI for the BCVA gains did not include 0.[21] Analyses were performed using WinBUGS V.1.4 (MRC Biostatistics Unit, Cambridge, UK).

Sensitivity analyses

Several sensitivity analyses were conducted to assess the robustness of the network meta-analysis. The results of a fixed effects and random effects model were compared. The impact of removing RCTs that did not capture outcomes at 6 months was analysed, as was the impact of excluding RCTs with substantially lower baseline BCVAs than the other RCTs. In addition, we evaluated the impact of including the Ranibizumab for Branch Retinal Vein Occlusion Associated Macular Edema Study (RABAMES),[22] in which the ranibizumab regimen was three doses at monthly intervals followed by a 3-month observation period. Finally, node-splitting analyses were used to compare the direct and indirect evidence of the efficacy of ranibizumab versus laser, ranibizumab versus dexamethasone implant and laser versus sham intervention. In the node-splitting analyses, the two-sided p value for the probability that the direct effect differed from the indirect effect was given by 2 (1—pr), if pr was ≥50% (where pr is the probability that the direct effect

was greater that the indirect effect); if pr was <50%, the p value for the probability that the direct effect differed from the indirect effect was 2pr.

RESULTS

Studies

Glanville et al[19] identified six potentially relevant studies of patients with BRVO: the Branch Vein Occlusion Study (BVOS)[7] Group trial, Battaglia Parodi et al,[8] GENEVA,[14] BRAVO,[23] Moradian et al[24] and Russo et al.[25] An additional study[26] included both individuals with BRVO and those with CRVO.[26] On full text evaluation, three studies met the inclusion criteria and were included in the analysis (BRAVO,[23] GENEVA[14] and Battaglia Parodi et al[8]). BVOS[7] was excluded because the efficacy data were presented at 36 months. The studies by Moradian et al[24] and Russo et al[25] were also excluded because they did not include two treatments of interest. Finally, the Kuppermann et al[26] trial was excluded because it did not present separate efficacy outcome results for BRVO and CRVO.

The updated systematic review identified eight potentially relevant RCTs; however, full-text screening found that only one of these, Tan et al,[27] met the inclusion criteria. In RABAMES,[22] patients received only three injections of ranibizumab 0.5 mg at monthly intervals, which were then followed by 3 months of observation. The number of injections was substantially lower than in the other studies evaluating ranibizumab, so the RABAMES[22] results were included only for sensitivity analysis. Three trials were excluded because these were extension studies[15 28 29] and three trials were excluded because they evaluated only one treatment of interest.[24 30 31] Manual searching identified three further trials (BRIGHTER,[32] COMRADE-B[33] and VIBRANT[12]).

The quality of the published studies is reported in table 1. In general, the studies were of good quality, with the exception of the study by Battaglia Parodi et al[8] which did not report most of the key quality assessment components.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the screening and selection process is presented in figure 1. The network of studies, comprising a total of 1743 adult patients for the efficacy analysis, is presented in figure 2. In total, seven RCTs were identified for the analysis: BRAVO,[9] VIBRANT,[12] Tan,[27] GENEVA,[14] BRIGHTER,[32] COMRADE-B,[33] and Battaglia Parodi et al.[8] RABAMES[22] was used in sensitivity analysis. Outcomes were reported at month 6 in all studies except the study by Tan et al,[27] for which outcomes were reported at month 12, and Battaglia Parodi et al,[8] for which outcomes were reported at months 3 and 12.

Treatment regimens

Three studies (Tan et al.,[27] BRIGHTER[32] and COMRADE-B[33]) reported results with a ranibizumab PRN regimen (table 2). BRAVO[9] was the only ranibizumab

Table 1 Quality appraisal of randomised controlled trials included in the network meta-analysis

Study	Was randomisation carried out appropriately?	Was concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Battaglia Parodi et al[8]	Unclear	Unclear	Yes	Unclear	Unclear	Yes	No
BRAVO[9 23]	Yes	Unclear	Yes	Yes	No	No	Yes
GENEVA[14 34]	Yes	Yes	Yes	Yes	No	No	Yes
RABAMES[22]	Yes	Yes	No	No	Yes	No	Yes
Tan et al[27]	Yes	Yes	Yes	Yes	Yes	No	Yes
VIBRANT[12]	Yes	Yes	Yes	Yes	No	No	Yes

BRIGHTER[32] and COMRADE-B[33] were not assessed for the risk of bias owing to limited study methodology being reported.

study in which results were reported after patients received six monthly doses of ranibizumab. Hence, for the purpose of this analysis, the ranibizumab treatment regimen is referred to as PRN. The mean number of injections in the first 6 months was 5.7 for aflibercept in VIBRANT[12]; this compared with 4.8 in BRIGHTER,[32] 4.9 in COMRADE-B[33] and 5.7 in BRAVO[9] for ranibizumab.

In Battaglia Parodi et al,[8] the mean BCVA gains from baseline at months 3 and 12 were used in the analysis as a proxy for the efficacy at month 6. We could not use the SDs from Battaglia Parodi et al[8] because these were reported on a non-linear transformation of the ETDRS. Instead, we assumed that the SD was the same as for BRAVO (13.2),[9] which is in the mid-range of SD values in table 2 (minimum: 7.5; maximum: 19.3).

Network meta-analysis

Eligibility criteria differed among RCTs (see online supplementary table 1). Therefore, patient-level data for three of the ranibizumab trials (BRAVO,[9] BRIGHTER[32] and COMRADE-B[33]) were reanalysed to match the key eligibility criteria from the VIBRANT aflibercept study[12] (ie, criteria relating to BCVA and duration of disease at baseline). Specifically, patients were excluded from the analysis if they had a baseline BCVA of less than 24 letters or a duration of disease of more than 12 months. Using these criteria, only three patients were excluded from BRAVO[9] and three patients were excluded from COMRADE-B,[33] but 91 of 448 (20.3%) patients were excluded from BRIGHTER.[32] The exclusion of these patients did not, however, create a major imbalance between treatment arms in BRIGHTER (see online supplementary tables 2 and 3). The baseline characteristics and efficacy outcomes of interest after this step are shown in table 2. Rates of increased IOP/OH are presented in table 3.

Statistically significant mean (95% CrI) changes in BCVA from baseline were found for ranibizumab monotherapy (+11.5 (7.5 to 15.9)), ranibizumab plus laser combination therapy (+10.1 (5.1 to 15.3)) and aflibercept (+10.2 (4.6 to 15.5)) when compared with laser therapy alone (table 4), and for ranibizumab monotherapy versus dexamethasone implant (+8.0 (4.0 to 11.9)). Pairwise ORs for gaining at least 15 letters and absolute letters gains from baseline in the random treatment effects model are presented in tables 5 and 6. Only ranibizumab monotherapy was statistically superior to laser therapy alone. OR (95% CrI) compared with laser therapy were 3.24 (1.03 to 12.56) for ranibizumab monotherapy and 3.07 (0.63 to 14.8) for aflibercept. Mean (95% CrI) BCVA letter gains were not statistically significant for ranibizumab monotherapy versus aflibercept (+1.4 letters (−5.2 to 8.5)) and the OR (95% CrI) for gaining at least 15 letters was 1.06 (0.16 to 8.94)). Patients treated with dexamethasone implant had statistically significant higher rates of IOP/OH than those receiving the anti-VEGF monotherapies (OR 13.1 (1.7 to 116.9)).
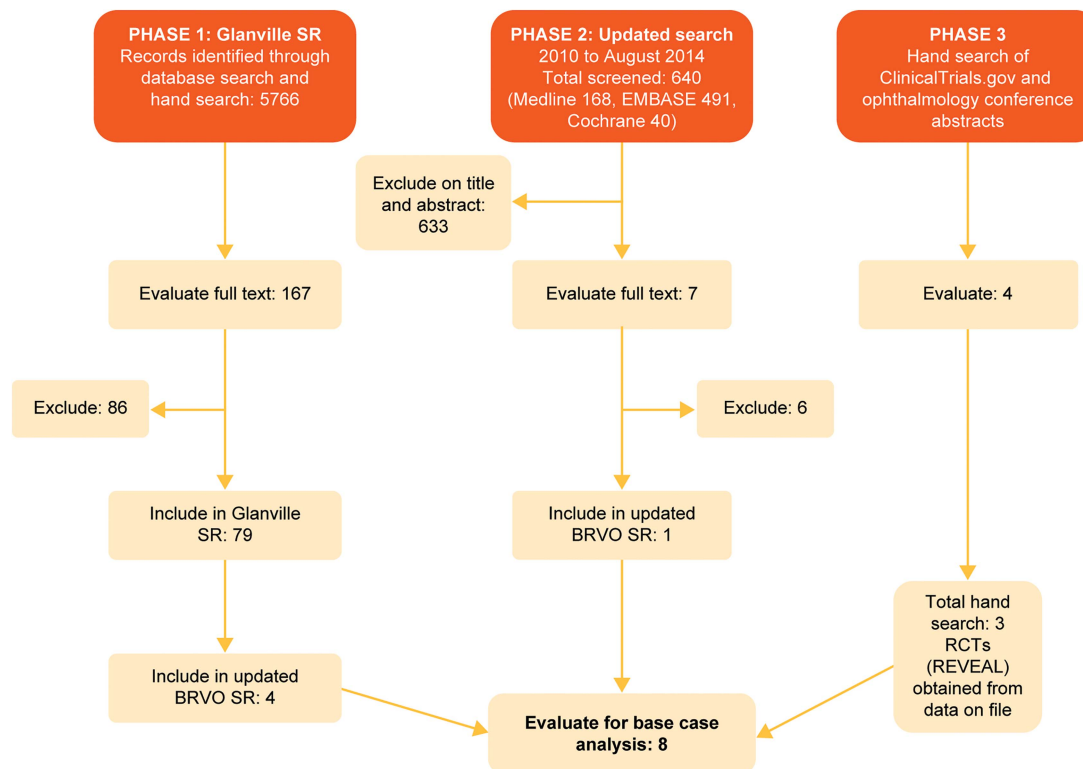
Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. BRVO, branch retinal vein occlusion; RCT, randomised controlled trial; SR, systematic review.

The probabilities of being the most efficacious treatment in the study network are presented in figure 3. The probability of being the most efficacious treatment based on BCVA letters gained was 54% for ranibizumab monotherapy, 30% for aflibercept and 16% for ranibizumab plus laser photocoagulation, and 0% for dexamethasone 0.7 mg implant. The probability that ranibizumab monotherapy is a better treatment than aflibercept is 67% (based on BCVA letter gained), which can be interpreted as follows: if 100 patients receive ranibizumab monotherapy in the right eye and aflibercept in the left eye, assuming the right and left eyes have the same baseline characteristics, on average, 67 patients would have a bigger gain observed in the right eye than in the left eye. The probability of being the most efficacious treatment based on the percentage of patients gaining at least 15 letters was 39% for aflibercept, 35% for ranibizumab monotherapy, 24% for ranibizumab plus laser photocoagulation, 2% for dexamethasone, 1% for sham intervention and <1% for laser monotherapy. On the basis of the percentage of patients gaining at least 15 letters, the probability that ranibizumab monotherapy is a better treatment than aflibercept is 53%.

Figure 2 Meta-analysis study network.
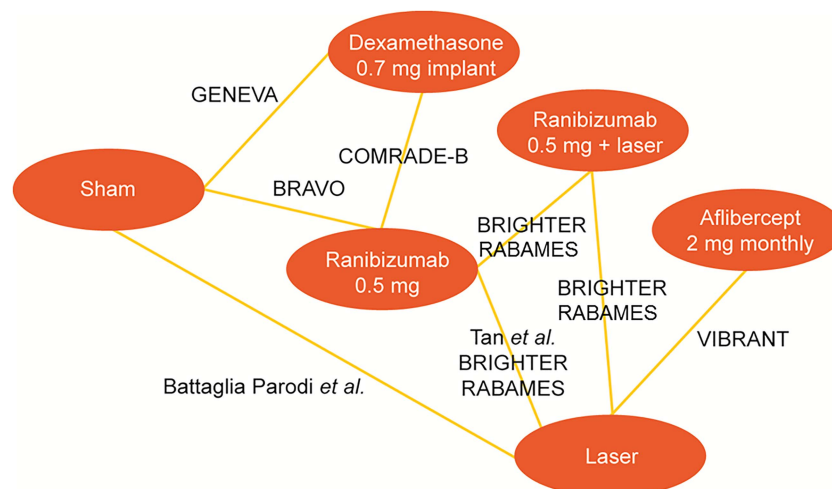
Table 2 Baseline patient characteristics and efficacy outcomes

Study	Treatment (dose)	Time end point measured (months)	Drug regimen	Mean number of injections/ implants	n	Baseline BCVA	Age (years)	Disease duration (months)	Baseline CRT (µm)	Patients gaining ≥15 letters (%)	BCVA increase (SD)
VIBRANT[12]	Aflibercept 2q4	6	6×monthly doses	5.7	91	58.6	67.0	1.4	559	53	17.0 (11.9)*
	Laser	6	–		90	57.7	63.9	1.4	554	27	6.9 (12.9)*
BRAVO†	Ranibizumab 0.5 mg	6	6×monthly doses	5.7	129	53.7	67.2	3.2	544‡	60	18.1 (13.2)
	Sham injection	6	–		131	55.0	65.1	3.5	488‡	29	7.3 (13.1)
Tan et al[27]	Ranibizumab 0.5 mg	12	6×monthly doses, then PRN	8.1	15	39.5	69.6	4.1	616‡	53	12.5 (19.3)
	Laser	12	–		21	46.2	66.7	3.5	519‡	19	−1.6 (18.2)
GENEVA[14]§	Dexamethasone 0.7 mg implant	6	1 implant at month 0	1.0	291	54.3	64.7	5.2	562	23	7.4 (7.6)§
	Sham procedure	6	–		279	54.8	63.9	5.1	539	20	4.9 (7.5)§
BRIGHTER†	Ranibizumab 0.5 mg	6	3×monthly doses, then PRN	4.8	142	58.9	63.9	3.4	554‡	50	16.3 (10.2)
	Ranibizumab 0.5 mg+laser	6	3×monthly doses, then PRN	4.5	143	56.7	66.7	3.2	582‡	48	15.0 (11.8)
	Laser		–		72	58.3	67.1	2.8	558‡	26	5.2 (14.7)
COMRADE-B†	Ranibizumab 0.5 mg	6	3×monthly doses, then PRN	4.9	124	57.9	65.6	2.0	537	61	17.0 (11.2)
	Dexamethasone 0.7 mg implant	6	1 implant at month 0		117	58.4	65.7	1.7	545	37	9.1 (12.5)
RABAMES[22]	Laser	6	–		10	59.0	68.8	5.0	571	20	2 (16.9)
	Ranibizumab 0.5 mg	6	3×monthly doses	~3.0	10	58.5	64.2	5.1	584	70	17 (12.5)
	Laser+ranibizumab 0.5 mg	6	3×monthly doses	~3.0	10	64.5	65.9	6.0	506	70	6 (9.3)
Battaglia Parodi et al[8]	Laser	3 and 12			33	65.6	NA	NA	NA	NA	9.7 (13.2)
	Control	3 and 12			35	64.6	NA	NA	NA	NA	11.1 (13.2)

Battaglia Parodi et al[8] decimal data are converted into BCVA letters.
*SDs were not reported in the VIBRANT publication,[12] but were provided by the authors of the study.
†Data for BRAVO, BRIGHTER, COMRADE-B is reported after patient-level data analysis.
‡Central foveal thickness.
§In GENEVA,[14] baseline characteristics were not split between patients with CRVO and those with BRVO. BCVA letters gained from the NICE assessment file entitled 'Evidence review: dexamethasone implants (Ozurdex) for macular oedema after retinal vein occlusion (2010)'. SE of the mean was graphically estimated.
2q4, 2 mg monthly; BCVA, best-corrected visual acuity (assessed in terms of Early Treatment Diabetic Retinopathy Study letters); BRVO, branch retinal vein occlusion; CRT, central retinal thickness; CRVO, central retinal vein occlusion; NA, not applicable; NICE, National Institute for Health and Care Excellence; PRN, pro re nata (as needed); RCT, randomised controlled trial.

Table 3 The proportion of patients reporting IOP and OH adverse events from baseline to month 6 by study and treatment group

Study	Ranibizumab 0.5 mg PRN, n/N (%)	Aflibercept 2q4, n/N (%)	Laser, n/N (%)	Sham, n/N (%)	Dexamethasone 0.7 mg implant, n/N (%)	Ranibizumab 0.5 mg PRN+laser photocoagulation, n/N (%)
BRAVO[9]	7/130 (5)			2/131 (2)		
VIBRANT[12]		2/91 (2)	0/92 (0)			
Tan et al[27]	Not reported		Not reported			
GENEVA[14]				4/276 (1)	82/288 (28)	
COMRADE-B[33]*	2/126 (2)				24/118 (20)	
BRIGHTER[32]	6/180 (3)		1/88 (1%)			12/183 (7)
Battaglia Parodi et al[8]			Not reported	Not reported		
RABAMES[22]	0/10 (0)		0/10 (0)			0/10 (0)
Total	15/446 (3)	2/91 (2)	1/190 (1)	6/407 (1)	106/406 (26)	12/193 (6)

Reported numbers are the sum of IOP and OH events.
BRAVO adverse events from the clinical study report.[9] BRIGHTER[32] and COMRADE-B[33] adverse events from data on file.
In GENEVA,[14] the adverse event split between BRVO and CRVO was done using the NICE assessment file entitled 'Evidence review: dexamethasone implants (Ozurdex) for macular oedema after retinal vein occlusion (2010)'.
*Treatment-emergent adverse events in the study eye.
2q4, 2 mg monthly; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; IOP, intraocular pressure; n, number of patients in treatment arm with adverse events; N, total number of patients in treatment arm; NICE, National Institute for Health and Care Excellence; OH, ocular hypertension; PRN, pro re nata (as needed).

Node-splitting analysis

The node-splitting results are presented in online supplementary table 4. The model showed an incremental gain (95% CrI) of 7.8 letters (1.8 to 13.8) for ranibizumab monotherapy versus dexamethasone implant from the direct evidence (COMRADE-B[33]), whereas the indirect evidence (all trials except COMRADE-B[33]) provided an incremental gain of 8.1 letters (0.8–15.5). This difference between direct and indirect evidence was non-significant (p=0.93). Similarly, there was no statistically significant difference between the direct[8] and indirect evidence of the relative efficacy of laser monotherapy versus sham intervention. The difference between direct and indirect evidence was higher when considering the incremental efficacy of ranibizumab monotherapy over laser monotherapy (2.5 letter difference between the indirect and the direct evidence), although this difference remained non-significant (p=0.61).

The choice of a random effects model (rather than a fixed effects model) was justified because of the heterogeneity among trials (between-study SD 1.2). However, the fixed effects model provided similar results to the random effects model, with ranibizumab monotherapy having a 63% probability of being the best treatment (in terms of letters gained) compared with 27% for aflibercept, 10% for ranibizumab plus laser and 0% for dexamethasone implant, laser and sham.

Sensitivity analyses

The sensitivity analyses results are summarised in figures 4 and 5 (see online supplementary materials). Including RABAMES[22] in the network had limited impact on the results. Mean (95% CrI) BCVA letters gained from baseline for ranibizumab monotherapy over aflibercept remained non-statistically significant (+1.7 (−4.7 to 9.1)), and the probability of ranibizumab monotherapy being the best treatment based on letters gained increased to 68%, compared with 27% for aflibercept and 5% for ranibizumab plus laser. The inclusion of RABAMES[22] slightly increased the ranibizumab numerical advantage in terms of percentage of patients gaining at least 15 letters (OR vs aflibercept 1.2 (0.3 to 7.8)). The probability that ranibizumab monotherapy was the best treatment increased from 35% to 40% (vs 30% for aflibercept, 28% for ranibizumab plus laser and 1% for dexamethasone implant). When data from the study by Battaglia Parodi et al[8] were excluded from the network, patients receiving ranibizumab monotherapy showed a non-significant mean (95% CrI) gain of

Table 4 Incremental BCVA letters gained at 6 months versus laser therapy alone (random treatment effects model)

Treatment	Incremental letters gained vs laser photocoagulation alone
Ranibizumab 0.5 mg PRN	11.5 (7.5 to 15.9)*
Ranibizumab 0.5 mg PRN +laser photocoagulation	10.1 (5.1 to 15.3)*
Dexamethasone 0.7 mg implant	3.5 (−1.6 to 9.1)
Aflibercept 2q4	10.2 (4.6 to 15.5)*
Sham	1.0 (−3.5 to 5.9)

*p<0.05.
Studies included in the base case analysis are VIBRANT,[12] BRAVO,[9] BRIGHTER,[32] COMRADE-B,[33] Tan et al,[27] Battaglia Parodi et al,[8] GENEVA.[14]
2q4, 2 mg monthly; BCVA, best corrected visual acuity; PRN, pro re nata (as needed).

Table 5 Pairwise ORs (95% CrI) for gaining ≥15 letters from baseline (random treatment effects model)

Comparator	Sham	Ranibizumab 0.5 mg PRN	Aflibercept 2q4	Laser photocoagulation	Dexamethasone 0.7 mg implant	Ranibizumab 0.5 mg PRN+laser photocoagulation
Sham	–					
Ranibizumab 0.5 mg PRN	3.53 (1.02 to 12.67)*	–	1.06 (0.16 to 8.94)	3.24 (1.03 to 12.56)*		
Aflibercept 2q4	3.38 (0.28 to 31.36)	0.95 (0.11 to 6.17)	–	3.07 (0.63 to 14.75)		
Laser photocoagulation	1.11 (0.17 to 5.68)	0.31 (0.08 to 0.97)*	0.33 (0.07 to 1.59)	–		
Dexamethasone 0.7 mg implant	1.22 (0.35 to 4.38)	0.35 (0.09 to 1.24)	0.36 (0.04 to 4.54)	1.11 (0.21 to 7.39)	–	
Ranibizumab 0.5 mg PRN+laser photocoagulation	3.18 (0.43 to 20.98)	0.89 (0.19 to 3.76)	0.94 (0.11 to 8.85)	2.87 (0.67 to 13.88)	2.59 (0.33 to 17.21)	–

*p<0.05.
Pairwise ORs indicate the relative treatment effect for the treatments compared in the network meta-analysis. A statistically significant OR greater than 1 indicates that the treatment in the corresponding row is superior to the treatment in the corresponding column.
Studies included in the base-case analysis are VIBRANT,[12] BRAVO,[9] BRIGHTER,[32] COMRADE-B,[33] Tan et al,[27] Battaglia Parodi et al,[8] GENEVA.[14]
2q4, 2 mg monthly; CrI, credible interval; PRN, pro re nata (as needed).

Table 6 Pairwise difference (95% CrI) for letters gained from baseline (random treatment effects model)

Comparator	Sham	Ranibizumab 0.5 mg PRN	Aflibercept 2q4	Laser photocoagulation	Dexamethasone 0.7 mg implant	Ranibizumab 0.5 mg PRN+laser photocoagulation
Sham	–					
Ranibizumab 0.5 mg PRN	10.6 (6.9 to 14.2)*	–				
Aflibercept 2q4	9.2 (1.7 to 16.1)*	−1.4 (−8.5 to 5.2)	–			
Laser photocoagulation	−1.0 (−5.9 to 3.5)	−11.5 (−15.9 to −7.5)*	−10.2 (−15.5 to 4.6)*	–		
Dexamethasone 0.7 mg implant	2.5 (−1.1 to 6.3)	−8.0 (−11.9 to −4.0)*	−6.7 (−14.0 to 1.3)	3.5 (−1.6 to 9.1)	–	
Ranibizumab 0.5 mg PRN +laser photocoagulation	9.2 (3.4 to 14.5)*	−1.4 (−6.3 to 3.1)	−0.0 (−7.4 to 7.6)	10.1 (5.1 to 15.3)*	6.6 (0.4 to 12.3)	–

*p<0.05.
2q4, 2 mg monthly; CrI, credible interval; PRN, pro re nata (as needed).
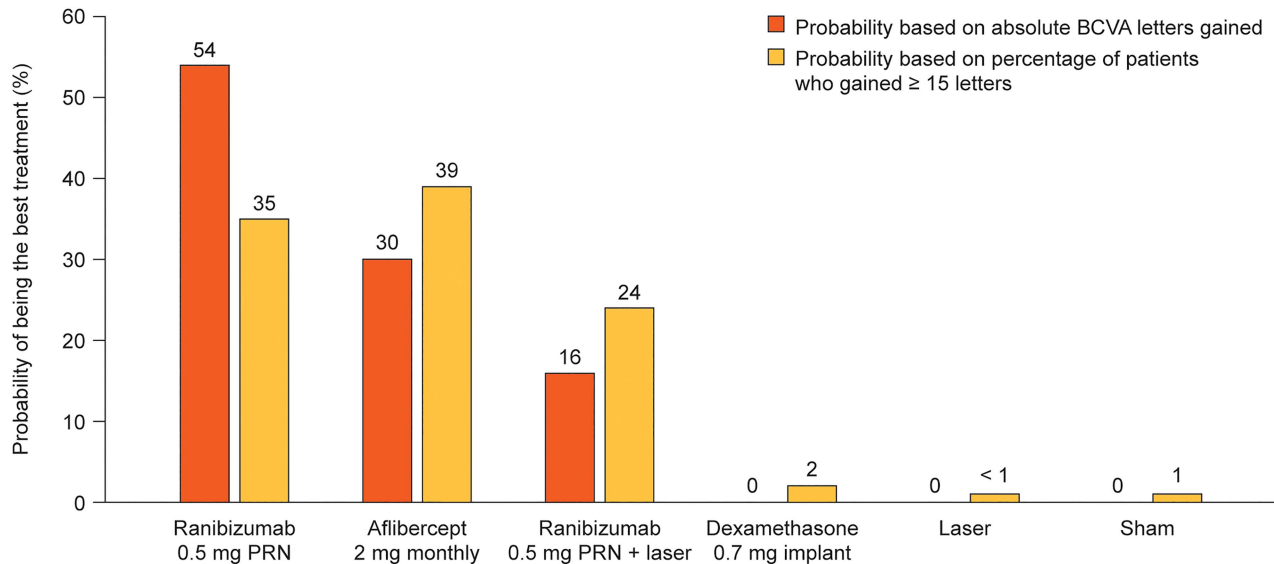
Figure 3 Probability that each treatment is the most efficacious in the study network. BCVA assessed in terms of ETDRS letters. BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, pro re nata (as needed).

1.4 letters (−6.3 to 9.5) over aflibercept. After excluding data from Tan et al[27] from the network, patients receiving ranibizumab monotherapy showed a non-significant mean (95% CrI) gain of 1.3 letters (−6.2 to 8.6) compared with those receiving aflibercept. When removing Tan et al or Battaglia Parodi et al,[8] ranibizumab monotherapy remained the agent with the highest probability of being the best treatment (52%, both). We attempted to analyse the rates of increased IOP/OH when results for ranibizumab and aflibercept were not combined. However, it was not possible to compare the relative rates of events between the two anti-VEGF therapies because the model did not converge.

DISCUSSION

Glanville et al[19] concluded that it was not possible to conduct a network meta-analysis in BRVO owing to
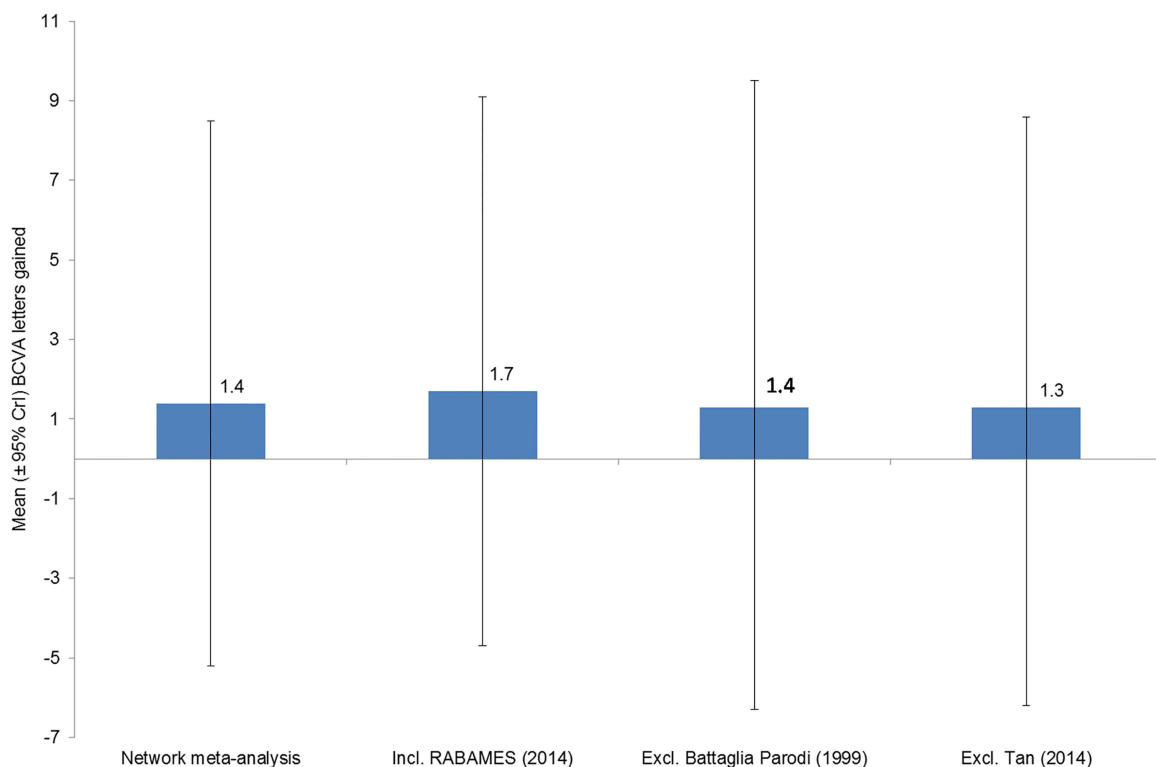
Figure 4 Sensitivity analysis: mean best corrected visual acuity (BCVA) letters gained from baseline for ranibizumab monotherapy over aflibercept.
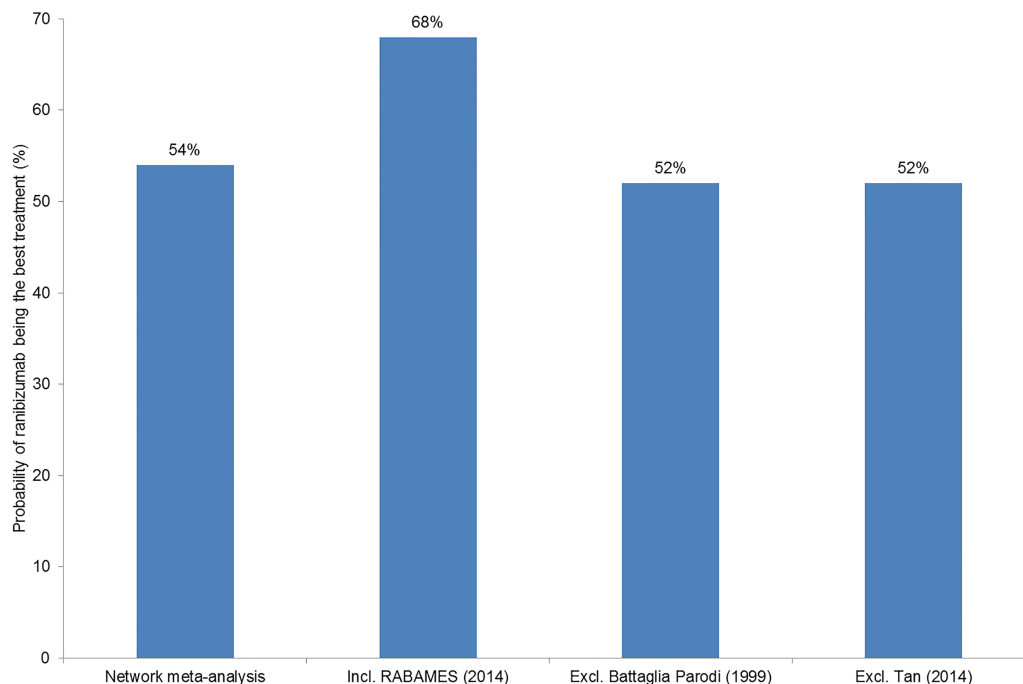
Figure 5 Sensitivity analysis: probability that ranibizumab monotherapy is the most efficacious treatment based on best corrected visual acuity (BCVA) letters gained from baseline.

interstudy differences in design and baseline characteristics. However, the BRVO analysis in their study included only three studies, BRAVO,[23] Battaglia Parodi et al[8] and GENEVA.[14] Since November 2010, when Glanville et al conducted the searches for their review, the preliminary results of new clinical trials were made available, allowing the network meta-analysis described here to be conducted. Specifically, BRIGHTER[32] enables comparison between laser therapy and ranibizumab monotherapy, and also between laser therapy and ranibizumab+laser combination therapy; COMRADE-B[33] allows direct comparison between ranibizumab monotherapy and dexamethasone implant, and VIBRANT[12] provides information on aflibercept versus laser therapy.

In general, the results from this network meta-analysis confirm the results from head-to-head clinical trials. In particular, our analysis confirms that anti-VEGF monotherapies are more efficacious than laser therapy, as shown in VIBRANT,[12] BRIGHTER,[32] RABAMES[22] and by Tan et al.[27] Our results also confirm the superiority, in terms of letters gained in BCVA, of ranibizumab monotherapy over dexamethasone implant, as shown in COMRADE-B.[33] A key finding was that the efficacy of laser was similar to sham intervention, suggesting that the role of laser in the treatment of BRVO should be reappraised. The CrIs were broad and there was no statistically significant difference between ranibizumab 0.5 mg PRN and aflibercept 2q4 in either letters gained or proportion of patients gaining more than 15 letters.

The results were shown to be robust in a number of sensitivity analyses, including an analysis from which trials that did not report outcomes at 6 months were excluded, and an analysis in which a trial with only three

injections in the first 6 months was included. In addition, there was no evidence of inconsistency between direct and indirect evidence. It was not possible to compare adverse event rates between ranibizumab monotherapy and aflibercept monotherapy because the model did not converge owing to the low incidence of increased IOP/OH. This meant that we had to merge ranibizumab and aflibercept treatments into an anti-VEGF therapy group. Similarly, the incidence of systemic adverse events was not analysed. The lack of convergence does not mean that there are no differences in increased IOP/OH rates between treatments: it could mean that the included studies did not have sufficient power to detect any such differences. A preliminary analysis indicated that two samples of 2525 individuals would be required to reach a power of 80% to detect significant differences between treatments if the event rates were 1–2%. Hence, analyses of real-world data could shed some light on the relative safety and tolerability of anti-VEGF and dexamethasone implant therapy and help to refine the full benefit-to-risk ratio of approved treatments for macular oedema secondary to BRVO.

The retreatment period for dexamethasone implant in the clinical trials was 6 months. Therefore, we used a 6-month perspective to evaluate the relative efficacy of dexamethasone implant. However, based on the GENEVA[14] and COMRADE-B[33] trials, the efficacy (and rate of increased IOP/OH) of dexamethasone implant peaks at month 2 before decreasing at month 6. While we cannot formally determine how dexamethasone implant would have performed with a 2-month retreatment regimen, the BCVA was 2.9 letters higher at month 2 than month 6 in GENEVA[14] and approximately 4.5 letters

higher at month 2 than month 6 in COMRADE-B.[33] Therefore, a bi-monthly retreatment regimen for dexamethasone implants may reduce the efficacy advantage of ranibizumab 0.5 mg PRN found in this network meta-analysis (+8.0 (4.0 to 11.9) letters vs dexamethasone implant). Additional trials assessing the efficacy and safety of bimonthly or trimonthly dexamethasone would be useful, allowing us to investigate this issue.

The results presented here indicate that the value of adjunctive laser photocoagulation therapy for macular oedema secondary to BRVO is uncertain. Our analysis was not able to demonstrate that the combination of laser and ranibizumab therapy provided higher efficacy gains than ranibizumab monotherapy. In addition, in BRIGHTER,[32] the mean (SD) number of ranibizumab injections was similar for the combination (4.5 (1.2) injections) and ranibizumab monotherapy arms (4.8 (1.0) injections). Therefore, it is not clear whether adjunctive laser therapy would decrease the ranibizumab injection costs.

The main challenge in any network meta-analysis is to compare studies that may have different populations (eg, owing to different inclusion/exclusion criteria). The key strength of the present analysis is that inclusion/exclusion criteria for baseline BCVA and duration of disease were matched in three trials containing anti-VEGF therapies. Those two variables (baseline BCVA and duration of disease) have shown to influence the outcome in RVO and need to be accounted for in order to reduce the risk of heterogeneity.[35] Indeed, when the ranibizumab clinical trials[9 32 33] were analysed without matching key inclusion/exclusion criteria to those of VIBRANT,[12] there were no differences in letters gained between ranibizumab 0.5 mg PRN and aflibercept 2q4 (0.0 letters (−6.7 to 7.5)). This demonstrates the importance of adjusting for baseline characteristics that influence clinical outcomes. In theory, a meta-regression with baseline BCVA and duration of disease as covariates could be run to account for heterogeneity. However, the coefficients for baseline BCVA or duration of disease did not converge (potentially because of the lack of degrees of freedom in the network).

The main limitation of the study is that, at the time of completion of this manuscript, two clinical trials were not yet published in the peer-reviewed literature and therefore, their quality could not be assessed. A second limitation was that the SEs of the BCVA gains in GENEVA[34] were only graphically estimated because these were not reported in the study. However, this assumption had a limited impact on the results. If we increase the SDs to 8.5 for the sham arm and to 8.7 for the dexamethasone implant arm (corresponding to a 95% CI of ±1 letter for the estimated mean in GENEVA),[34] the results remain similar: the ranibizumab 0.5 mg PRN advantage over dexamethasone implant remains at 8.0 (4.0 to 11.9) letters. A further limitation was that the definition of increased IOP was not usually reported in the publications and it was not possible to

assess whether there were substantial differences and, if so, whether the differences were relevant. Finally, data from only a limited number of trials were included in this analysis, and future analyses will be strengthened once additional clinical trial data becomes available.

CONCLUSIONS

This Bayesian network meta-analysis confirmed the superiority of ranibizumab monotherapy over dexamethasone implant or laser for the treatment of macular oedema secondary to BRVO, and showed that there were no statistical differences between ranibizumab monotherapy and aflibercept.

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