Intravitreal ranibizumab (Lucentis) for the treatment of diabetic macular edema: a systematic review and meta-analysis of randomized clinical control trials


CRD summary
The authors concluded that intravitreal ranibizumab and ranibizumab combined with focal/grid laser were safe and more effective than focal/grid laser alone or non-drug treatment for treating negative effects of diabetic macular edema at 12 and 24 months follow-up. Limitations of the evidence base mean that these conclusions may not be wholly reliable.

Authors' objectives
To evaluate the therapeutic effect and safety of intravitreal ranibizumab or ranibizumab combined with focal or grid laser in diabetic macular oedema.

Searching
Central Register of Controlled Trials (CENTRAL), PubMed and EMBASE were searched to August 2011 without date or language restrictions. Search terms were reported. Clinical registries and search engines were searched to locate further studies.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared ranibizumab or ranibizumab combined with focal/grid laser with non-drug controls or focal/grid laser therapy for the treatment of diabetic macular oedema. Primary eligible outcomes were change in best-corrected visual acuity and central macular thickness from baseline at 12 and 24 months. The secondary outcome was incidence of adverse events. Trials that included patients who received focal/grid laser prior to intravitreal ranibizumab were excluded.

Across the trial arms, doses of ranibizumab ranged from 0.3mg to 0.5mg (frequency of administration not reported). All trials reported reduced vision or visual acuity resulting from diabetic macular oedema at baseline; most trials prespecified letter score ranges of best-correct visual acuity as eligibility criteria for patient enrolment.

Two reviewers selected studies for inclusion; discrepancies were resolved by discussion.

Assessment of study quality
Risk of bias was assessed using Cochrane criteria for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other bias. A rating of yes (low risk of bias), no (high risk of bias) or unclear (unknown risk of bias) was assigned for each criterion.

Two reviewers assessed study quality. Authors were contacted for any information rated unclear; the rating was kept as being unclear if the authors did not respond within four weeks.

Data extraction
Data were extracted to calculate mean differences (MD) or odds ratios (OR), with 95% confidence intervals (CIs). Data from treatment and control groups were extracted independently by two reviewers. Authors were contacted for information where necessary.

Methods of synthesis
Estimates were pooled in a fixed-effect or random-effects meta-analysis according to the level of statistical heterogeneity indicated. Statistical heterogeneity was assessed using the I² statistic (I²>50% was seen to indicate substantial heterogeneity). Subgroup analyses were performed for the 12 and 24 month follow-up periods.

Results of the review
Four RCTs were included in the review (1,476 patients according to the study characteristics table, range 126 to 854 patients per trial). Total length of follow-up ranged from 12 to 24 months. Two trials had low risk of bias for all seven domains assessed. One trial had an unclear risk of bias for allocation concealment but low risk for all other domains. The other trial had low risk of bias for incomplete outcome data, selective reporting and other bias; this trial's risk of bias for all other domains was assessed as being unclear.

**Ranibizumab versus non-drug controls:** Compared with non-drug controls, ranibizumab groups demonstrated a significantly greater increase in best-correct visual acuity from baseline to 12 months (MD 7.50, 95% CI 3.43 to 11.58; two trials; I²=55%) and significantly greater reduction in central macular thickness (MD -94.42, 95% CI -174.22 to -14.62; two trials; I²=82%).

Two trials reported no statistically significant differences between ranibizumab and non-drug controls regarding the incidence of eye pain, hypertension and arterial thromboembolism.

**Ranibizumab and focal/grid laser versus laser alone:** Compared with those treated with laser alone, ranibizumab-laser combination groups demonstrated a significantly greater increase in best-correct visual acuity from baseline at 12 months (MD 5.83, 95% CI 4.07 to 7.59; two trials; I²=0%) and at 24 months (MD 3.95, 95% CI 1.07 to 6.84; two trials; I²=8%). At 12 months, significantly greater reduction in central macular thickness (MD -46.82, 95% CI -83.98 to -9.65; two trials; I²=69%) was observed among ranibizumab-laser combination groups versus groups that received laser alone.

**Ranibizumab versus ranibizumab and focal/grid laser:** None of the data from relevant trials were amenable to meta-analysis. Individual trials demonstrated no significant differences between the groups for change in best-corrected visual acuity at 12 and 24 months and reduction in central macular thickness at 12 months. The trial with the poorest quality reported that reduction in central macular thickness at 12 months was significantly greater among ranibizumab-laser combination groups compared with those that received ranibizumab alone.

**Authors' conclusions**

Intravitreal ranibizumab and ranibizumab combined with focal/grid laser were well tolerated and more advantageous than focal/grid laser alone or non-drug treatment for reducing central macular thickness and improving best-corrected visual acuity in diabetic macular oedema during 12 and 24 months follow-up. Intravitreal ranibizumab may be equivalent to ranibizumab combined with focal/grid laser.

**CRD commentary**

The review question was clear and inclusion criteria appeared sufficiently replicable. Relevant databases and online sources were accessed and there were no language restrictions, which reduced the likelihood of language bias. The lack of a date restriction during the search also reduced the risk of relevant trials being missed. Efforts were made to reduce error and bias during the review processes. Suitable quality assessment criteria were employed; results showed that most of the included trials had low risk of bias for six or more of the seven quality domains assessed. Study details were presented and methods of analysis seemed appropriate given the small number of trials. Substantial statistical heterogeneity was indicated in three of the five meta-analyses with statistically significant results.

This seemed to be a well-conducted review but limitations of the evidence base mean that the authors' conclusions may not be wholly reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that in comparison with non-drug treatment, ranibizumab was safe, generally tolerated and could be considered as first choice of treatment for diabetic macular oedema.

**Research:** The authors stated that further examination of the diversity between interventions and development of standard guidelines for the treatment of diabetic macular oedema should be achieved through a substantially larger number of RCTs.

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