The LUCIDATE study – final report to National Research Ethics Service and MHRA

Full title of study:	Diabetic macula oedema: A prospective randomised study comparing the detailed functional and anatomical changes of repeated pan anti-VEGF therapy with ranibizumab versus conventional macular laser therapy.
Name of main REC:	Central London REC 4
REC reference number:	10/H0715/40
Date of favourable ethical opinion:	08/10/2010
Sponsor:	Moorfields Eye Hospital NHS Foundation Trust
EudraCT Number:	2010-021722-35

Methodology

The LUCIDATE study (LUCentis In Diabetic macular oedema – A Treatment Evaluation) was a randomised clinical trial designed to compare the detailed anatomical and functional effects of repeated pan anti-VEGF inhibition with ranibizumab with the effects of standard macular laser therapy after 48 weeks of treatment.

This trial was a single centre, parallel group, phase IV (clinical use) exploratory trial with imbalanced randomisation (2:1 ranibizumab:laser) and investigator masking conducted at Moorfields Eye Hospital.

Objectives

The study had a number of prospectively defined exploratory anatomical and functional outcomes, reported at baseline, 12, 24 and 48 weeks:

Functional measures

1. Best-corrected visual acuity
2. Color contrast sensitivity: protan and tritan thresholds
3. Microperimetric retinal sensitivity: mean 4° and 12° sensitivity
4. Electrophysiological parameters: pattern electroretinogram (PERG) P50 amplitude and implicit time, N95 amplitude; full field electroretinogram (ERG) rod and cone a and b wave amplitudes and implicit times, multifocal electroretinogram (mfERG) distribution of amplitudes

Anatomical measures

1. Optical coherence tomography (OCT) quantitative parameters: macular thickness and volume

2. OCT qualitative changes: presence of features of diabetic macular oedema (DMO) in inner and outer retina (cysts, cystoids edema and hyperreflective foci); neurosensory retina changes (external limiting membrane (ELM) interruptions, photoreceptor inner segment-outer segment (IS-OS) junction abnormalities); vitreomacular interface abnormalities (epiretinal membrane (ERM), vitreomacular traction (VMT), macular or lamellar hole).
3. Fluorescein angiography: greatest linear diameter (GLD) and area of foveal avascular zone (FAZ); degree of perifoveal capillary loss (PFCL)
4. Colour fundus photography: grade of diabetic retinopathy

Results

Patient Disposition and Demographics

Subjects were recruited from November 2010 to July 2011. The final follow up visit was in July 2012. Twenty five patients were randomized to receive ranibizumab 0.5 mg; 12 to receive macular laser. The 48 week study period was completed by 22 (88%) patients in the ranibizumab arm and 11 (92%) patients in the laser arm. Their baseline characteristics were comparable. There was no significant change in blood pressure or systemic diabetes control over the study period.

Efficacy

Mean (SD) best corrected visual acuity at baseline in the ranibizumab group was 70.4 (4.9) letters and 63.8 (5.7) letters in the laser group. This improved to 76.4 (8.5) letters in the ranibizumab group at 48 weeks but decreased to 62.9 (10.6) letters in the laser group (p=0.083 ANCOVA). This represented a 6 letter gain for ranibizumab versus a loss of 0.9 letters for laser.

Retinal sensitivity, measured by microperimetry, in the central 4° improved from 10.8 (3.7) to 14.0 (4.2) dB in the ranibizumab group and from 10.2 (3.8) to 12.1 (3.4) dB in the laser group (p=0.19). Sensitivity in the central 12° improved from 13.3 (2.7) to 15.7 (2.8) dB in the ranibizumab treated subjects and for laser treated subjects the improvement was from 13.4 (2.5) to 14.5 (2.0) dB (p=0.12).

Colour contrast sensitivity for red colours improved for ranibizumab treated subjects from 21.4 (22.5) % to 18.0 (16.9) % but worsened in the group receiving laser from 22.9 (22.8) % to 31.0 (35.0) %. The sensitivity to contrast for blue colours also improved for ranibizumab treated subjects from 80.7 (29.6) % to 69.9 (34.5) %. There was improvement, to a lesser degree, in laser treated subjects from 88.9 (20.7) % to 85.8 (25.0) %

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Results of electrophysiological tests such as the pattern electroretinogram (PERG) showed similar trends. Laser treated subjects experienced a decline of 0.13 µv (10.5%) in the P50 component of the PERG from baseline to 48 weeks, while ranibizumab treated subjects showed minor decline (0.04 µv; 2.9%).

Multifocal ERG responses at central and peripheral locations were compared between ranibizumab treated and laser treated groups. The changes in response amplitude were variable in both subject groups at 12, 24 and 48 weeks. All subjects from both ranibizumab treated and laser treated groups demonstrated moderate to severely reduced central responses i.e. moderate to severe central macular dysfunction, at baseline. The majority of subjects, approximately 60%, from the laser treated group demonstrated additional mild to moderate peripheral macular dysfunction at baseline, compared with 10% in the ranibizumab treated group. Thirty four percent of ranibizumab treated subjects and 18% of laser treated subjects experienced mild to moderate increase in central responses (i.e. central macular function) at 48 weeks. Fourteen percent of ranibizumab treated subjects and 27% of laser treated subjects experienced reduction in central responses at 48 weeks. The remaining subjects (52% of ranibizumab treated and 55% of laser treated) showed no change in central or peripheral responses from baseline to 48 weeks.

Structural imaging studies

Using automated measurements, ranibizumab treated subjects showed a decrease in the central OCT subfield thickness from 455 (79) µm to 324 (78) µm (reduction of 132 (98) µm) while laser treated subjects decreased from 488 (96) µm to 385 (98) µm (reduction of 103 (88) µm) (p=0.06 at 48 weeks, ranibizumab vs. laser). This suggests ranibizumab leads to greater reductions in retinal thickness than laser.

The prevalence of the morphological features of diabetic macular oedema were reported. The prevalence of subretinal fluid in the central subfield decreased in the ranibizumab arm but not the laser arm by 48 weeks. There was no clear evidence of a treatment effect in either group on cysts or cystoid oedema in the inner or outer retina either in the central subfield or the four surrounding (inner) subfields. All subjects had an abnormal foveal depression at baseline. In the laser group, 9% of subjects (1/11) had a normal foveal depression by 48 weeks but in the ranibizumab group this was 40% (9/22 subjects). The two groups were comparable at baseline in terms of the prevalence of interruptions in the lines representing the external limiting membrane or inner segment-outer segment (IS/OS)

junction (ellipsoid layer), but at 48 weeks the ranibizumab group showed a significantly lower prevalence of interrupted ELM compared with laser (P=0.01, Fisher's exact test). The prevalence of interrupted IS/OS junction in the laser group increased while the ranibizumab group decreased (P=0.14). In the ranibizumab group, 5 subjects (22.7%) had an epiretinal membrane at baseline; 4 subjects in the laser group (36.4%). At 48 weeks there was no significant difference in these figures. One subject in the ranibizumab group had an incomplete PVD identified at baseline, which persisted until 48 weeks. No subjects had lamellar hole, macular hole or vitreomacular traction at any time point.

Four-field colour photographs were graded at baseline and 48 weeks to obtain the numerical grade of diabetic retinopathy. One subject in the laser group worsened by one grade, 6 remained the same and 4 improved by one grade. Two of the ranibizumab group worsened by one grade; 1 by three grades and 10 remained the same. Seven improved by one grade and 2 by 2 grades.

Safety outcomes

Ocular and non-ocular adverse events occurred in both treatment groups, but there were no cases of endophthalmitis in either treatment arm. Ocular adverse events occurred more frequently in the ranibizumab arm (19 vs. 1) and were related to the injection procedure itself. There were more non-ocular adverse events in the ranibizumab arm (44 vs. 17), although the frequencies of the most common of these were similar in the two arms. The most common were upper respiratory tract infections and urinary tract infections. No serious adverse events were related to the study drug or injection procedure. There were 2 deaths reported during the study (1 per treatment arm), neither of which related to the study drug.

All subjects had a baseline foveal avascular zone (FAZ) greatest linear dimension (GLD) less than 1000 µm on fluorescein angiography. In both groups there was a small increase in FAZ area from baseline to 48 weeks (ranibizumab: 0.255 (0.102) mm^2 to 0.321 (0.111) mm^2; laser: 0.346 (0.163) mm^2 to 0.432 (0.192) mm^2, P=0.476 ANCOVA). Perifoveal capillary loss (PFCL) worsened by at least one grade in 15/40 (37.5%) of quadrants graded in the laser group and in 24/84 (28.6%) of quadrants in the ranibizumab group. The changes in grade for each quadrant were added to give a single score per subject and there was no difference in score between the two groups (P=0.65, Rank-sum test). Rod system function was evaluated by the dark-adapted ERGs. There was no change identified in the dim flash ERG b-wave (DA 0.01) in either group over 48 weeks. The mean a-wave amplitude in the scotopic brighter flash ERG (DA 11) decreases in the ranibizumab group from 249 µv to 228 µv with

no change in peak time, while the b-wave amplitude decreases from 387 μv to 368 μv, again with no change in peak time. None of the changes were clinically significant in any patient. The laser group show no noticeable change over the study. There were no evident changes in cone system function. In summary the electrophysiology results show no evidence of generalised dysfunction as a result of ranibizumab treatment.

Summary

The LUCIDATE study recruited to its intended target and a high proportion of subjects completed follow-up to the study endpoint at 48 weeks. The study reported on all prospectively defined exploratory outcome measures. The results showed a trend towards improved retinal function and structure with ranibizumab treatment compared with laser. Statistical significance for most of the reported outcomes was not reached because of the small sample size. No new safety concerns arose during the study. During the study period, ranibizumab went through the process of NICE approval for use in the NHS and is now available to treat some patients with DMO.

Dissemination of results

This exploratory data has been submitted for publication in the American Journal of Ophthalmology and will provide a valuable data set for ongoing research in this subject area in the ophthalmic community. Participants will be informed of the results of the study via an amended version of this document.