Intravitreal aflibercept compared with panretinal photocoagulation for proliferative diabetic retinopathy: the CLARITY non-inferiority RCT

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Scientific summary

The CLARITY non-inferiority RCT

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Scientific summary

Background

Proliferative diabetic retinopathy (PDR) is characterised by the development of new vessels that, if untreated, can result in significant complications including vitreous haemorrhage, tractional retinal detachment and resultant severe visual loss. Approximately 6% of people with diabetes mellitus suffer from PDR, which translates into a globally affected population of 24.9 million and underlines the huge public health burden of the condition. Panretinal photocoagulation (PRP) has been the standard of care for this condition for over four decades. In PRP, laser burns are applied to the peripheral retina to destroy the retinal tissue to reduce the hypoxic stimulus that drives growth factor production, principally vascular endothelial growth factor (VEGF), which in turn causes the regression of retinal neovascularisation (NV). PRP is very effective in reducing visual loss compared with no treatment. However, PRP is a destructive procedure with well-documented side effects. Approximately 13% of those treated with PRP develop visual loss because of the development of, or worsening of, pre-existing macular oedema. In addition, PRP may lead to transient or permanent loss of visual function, including peripheral visual field defects, night vision loss, loss of contrast sensitivity, and progression of visual loss in nearly 5% of individuals despite appropriate treatment. Approximately 4% of PDR patients require vitrectomy because of the severity of PDR and/or non-response to PRP. There is therefore a need for novel treatments that could either replace or delay the need for PRP for PDR.

Recent intravitreal therapies targeting VEGF, such as pegaptanib (Macugen® Eyetech, New York, NY, USA/Pfizer, New York, NY, USA), ranibizumab (Lucentis® Genentech, S. San Francisco, CA, USA/Roche, Basel, Switzerland), bevacizumab (Avastin® Genentech, S. San Francisco, CA, USA/Roche, Basel, Switzerland) and aflibercept (Eylea® Regeneron, Tarrytown, NY, USA/ Bayer Pharma AG, Berlin, Germany), have introduced a paradigm shift in the management of a wide array of ocular diseases, including neovascular age-related macular degeneration, diabetic macular oedema (DMO) and retinal vein occlusions. Anti-VEGF treatment has superseded macular laser treatment and is now the standard of care in patients with centre-involving DMO. However, therapeutic options for PDR remain limited to PRP despite several clinical and preclinical studies indicating that VEGF is the key causative factor of retinal NV. Recent evidence also indicates that monthly anti-VEGF treatment can reduce the severity of and delay the progression of diabetic retinopathy over 24 months. Moreover, after the initiation of this study, a well-designed trial reported the visual outcome at 24 months with repeated ranibizumab therapy as non-inferior to PRP in eyes with PDR (Writing Committee for the Diabetic Retinopathy Clinical Research Network, Gross JG, Glassman AR, Jampol LM, Inusah S, Aiello LP, *et al.* Panretinal photocoagulation vs. intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA* 2015;**314**:2137–46). However, there is no evidence of the role of aflibercept in PDR. Aflibercept blocks all VEGF-A isomers, VEGF-B and placental growth factor but it has not been previously evaluated in PDR. It may be an effective alternative to PRP with fewer visual function adverse events at 12 months.

We therefore conducted a multicentre randomised active controlled non-inferiority trial to investigate the efficacy and cost-effectiveness of intravitreal aflibercept on clinical outcomes in PDR: the clinical efficacy and mechanistic evaluation of aflibercept for proliferative diabetic retinopathy study.

Objectives

The specific research questions addressed in this trial in eyes with PDR were:

- Is the best corrected visual acuity (BCVA) at 52 weeks after aflibercept therapy no worse than with PRP treatment?
- Is intravitreal aflibercept beneficial in terms of other clinical outcomes compared with PRP?
- What is the cost-effectiveness of intravitreal aflibercept as compared with PRP?
- What are the likely mechanisms of actions of intravitreal aflibercept in PDR?

Methods

Design

This multicentre, prospective, individually randomised, single-masked, active-controlled non-inferiority trial with concurrent economic evaluation evaluated the clinical efficacy and cost-effectiveness of intravitreal aflibercept compared with PRP at 52 weeks. A subset of the participants also took part in a mechanistic evaluation substudy.

Setting

The study was conducted in the ophthalmology departments of 22 NHS trusts.

Participants

Adults with treatment-naive PDR or eyes with persistent retinal NV despite complete initial PRP with no evidence of macular oedema confirmed on spectral-domain optical coherence tomography were included in the study. Eyes with vitreous haemorrhage preventing laser treatment, vitrectomised eyes, eyes with iris or angle NV and neovascular glaucoma were excluded. Patients with blood pressure > 170/110 mmHg or a glycated haemoglobin level of > 12% and serious concomitant disease (e.g. renal failure or post-renal transplant) were also excluded.

Interventions

Participants were individually randomised to receive intravitreal injections of aflibercept or PRP in a 1 : 1 allocation ratio. Participants in the aflibercept arm were given a loading phase of three 4-weekly aflibercept injections and then this was repeated every 4 weeks based on predefined retreatment criteria depending on the level of regression and reactivation. Participants in the PRP arm received initial repeated PRP sessions until completion and were reviewed 8 weekly and were retreated based on identical predefined retreatment criteria. The trial included a mechanistic substudy of 40 participants who underwent retinal oximetry and image analysis at baseline, 12 and 52 weeks to explore the effect of aflibercept and PRP on the retina and blood vessels.

Follow-up

The participants were followed up for 52 weeks.

Clinical outcomes and analysis

The primary outcome was the mean change in adjusted BCVA at 52 weeks utilising a linear mixed-effects model that took into account the visual acuity outcomes at 12 and 52 weeks and excluded eyes with more than 3 standard deviations (SDs) of visual acuity fluctuation because of vitreous haemorrhage. The primary outcome was analysed in both the intention-to-treat (ITT) and per-protocol (PP) populations. Other outcomes at 52 weeks included differences in low-luminance visual acuity and contrast sensitivity, peripheral visual fields, regression of new blood vessels, safety profile, cost-effectiveness, treatment outcomes and satisfaction and quality-of-life questionnaires.

The target sample size was 220 and the non-inferiority margin was –5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. The primary analysis was both an ITT analysis and PP analysis and non-inferiority had to be observed in both analyses before non-inferiority could be concluded and superiority be evaluated.

Economic analysis

From a public sector multiagency perspective that covers health and social care services, evaluations of the cost-effectiveness of aflibercept compared with PRP were conducted as part of the trial. A primary cost-effectiveness analysis was undertaken and its effectiveness was measured in terms of BCVA. A secondary exploratory cost–utility analysis was also carried out and utility measured in terms of quality-adjusted life-years (QALYs). We collected hospital- and community-based health and social care service use using a Client Service Receipt Inventory completed by the study participants. We undertook economic evaluation on participants with complete cost and outcome data.

Mechanistic study

Retinal oximetry before and after aflibercept therapy was compared with the change observed after PRP at 52 weeks. The changes in capillary non-perfusion, and vessel calibre and new vessel regression, were also compared between arms.

Results

We recruited 232 patients between August 2014 and December 2015. The study had a good retention rate and compliance rate. The proportion of patients who received treatment in accordance with protocol was 94% (109/116) in the aflibercept arm and 97% (113/116) in the PRP arm. Economic evaluation was undertaken on 202 participants (101 per arm) with complete cost and outcome data. This represents 96.7% of the clinical sample included in primary outcome ITT analysis.

Clinical results

In the ITT analysis strategy, both PP and ITT analyses showed that aflibercept was non-inferior and superior to PRP. A total of 232 participants (116 per arm) were recruited between August 2014 and November 2015. A total of 221 and 210 participants contributed to the ITT model and PP analysis, respectively. Aflibercept was non-inferior and superior to PRP in both the ITT population [mean BCVA difference 3.9 letters, 95% confidence interval (CI) 2.3 to 5.6 letters; $p < 0.0001$] and the PP population (difference 4.0 letters, 95% CI 2.4 to 5.7 letters; $p < 0.0001$). The proportion of patients with ≥ 10-letter improvement and with baseline BCVA ≤ 90 was 5% (5/101) in the aflibercept arm, compared with 2% (2/95) in the PRP arm (difference between arms was 2.8%, 95% CI –3.1% to 9.1%; $p = 0.45$). The proportion of patients with ≥ 10-letter worsening was 5% (5/107) in the aflibercept arm, compared with 15% (16/104) in the PRP arm (difference between arms was 10.7%, 95% CI 2.6% to 19.3%; $p = 0.009$). There was 5% (5/107) of patients with ≥ 15-letter worsening in the aflibercept arm and 6% (6/104) in the laser arm (difference between arms was 1.1%, 95% CI –5.5% to 7.9%; $p = 0.72$). Binocular Esterman scores showed significant worsening in the PRP arm. This was also reflected in lower binocular visual acuity scores in the PRP arm. Other visual function tests did not vary between arms. There were no differences between the secondary outcomes of vision-related quality of life [National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) and Retinopathy-Dependent Quality-of-Life Questionnaire (RetDQoL)] between arms but patient satisfaction was higher in the aflibercept arm measured using the Retinopathy Treatment Satisfaction questionnaire, the adjusted mean difference was 3.0 (95% CI 0.4 to 5.5; $p = 0.022$). The difference in proportions of total regression favouring the aflibercept arm was 30% (95% CI 16% to 42%; $p < 0.0001$) at 52 weeks. A significantly higher proportion of patients in the PRP arm remained with PDR (level 61 or above) than in the aflibercept arm at both 12 and 52 weeks.

There were no safety concerns. New-onset macular oedema and vitreous haemorrhage were significantly more prevalent in the PRP arm. By 52 weeks, aflibercept arm patients received a mean standard deviation (SD) of 4.4 (1.7) injections (95% CI 4.1 to 4.7 injections) [median interquartile range (IQR) 4.0 (3.0–5.0)] including the three mandated loading doses. The mean number of aflibercept injections in treatment-naive patients was 4.6 (1.6) [median (IQR) 4 (3–6)] while non-naive patients received a mean of 4.1 injections (SD 1.8) [median (IQR) 4.0 (3.0–4.8)]. In the PRP arm, 78 (69%) received multispot laser and the remaining received single spot laser. From week 12, 75 patients (65%) in the PRP arm required supplemental PRP.

Economic results

From a public sector multiagency perspective that covers health and social care services, treatment with aflibercept costs more in terms of total resource use (mean adjusted total additional cost per patient = £5475, bootstrapped 95% CI £5211 to £5750) than PRP laser treatment over a 12-month follow-up period. Sensitivity analysis, in which the costs of aflibercept were varied from the list price to reflect possible NHS Patient Access Scheme (PAS), showed this to be the case at any price because of the higher cost of the

purchase and administration of aflibercept and associated hospital costs than with PRP treatment. If society is willing to pay £1400 for an additional 1-point improvement in BCVA, then aflibercept has a 56.60% probability of being cost-effective at the list price of £816. From 20% through to 100% PAS, results showed 100% probability of aflibercept being cost-effective at the hypothetical societal willingness-to-pay threshold of £1400. Participants who received aflibercept gained benefits in BCVA (mean adjusted BCVA = 3.93, bootstrapped 95% CI 3.84 to 4.02) but at an increased cost. No statistically significant difference was found in self-reported generic HRQoL [EuroQol-5 Dimensions, 3-level version) or in terms of capability (Investigating Choice Experiments Capability Measure for Adults). It may be that these measures were not sufficiently sensitive to pick up any changes over the 12-month follow-up period between groups. We have undertaken a secondary exploratory cost–utility analysis (i.e. cost per QALY analysis). Evidence is mixed, but points to the EQ-5D-3L not being sufficiently sensitive to be useful in studies of visual impairment. Our study results speak for themselves – we ended up dividing a mean adjusted cost difference of £5475 by an extremely small and non-statistically significant mean adjusted QALY difference of –0.022. This yields a cost per QALY of –£248,863, in which there is not much confidence. Given that a positive significant difference was observed in the BCVA for the intervention group, we interpreted this as the EQ-5D-3L not being sufficiently sensitive in this context. The vision-specific self-reported HRQoL measure (RetDQoL and NEI-VFQ-25, non-preference based) also showed no statistically significant difference over the study period between groups.

Mechanistic results

The mechanistic study showed that there were no differences between arms in the change in oxyhaemoglobin saturation levels in the retinal arteries and veins. In addition, the change in non-perfusion was also not significant between arms. New vessel regression in the fundus was more significant with aflibercept. The reduction from baseline in quantifiable area of new vessels was significantly greater in the aflibercept arm than in the PRP arm at 12 weeks ($p = 0.019$). By 52 weeks, this difference between arms in the area of new vessels was smaller and not significant ($p = 0.45$).

Conclusions

The study provides substantial evidence for the efficacy and safety of intravitreal aflibercept in PDR and indicates that the visual acuity and anatomical outcomes at 1 year are superior to conventional laser therapy, but at an additional cost. Long-term outcomes need to be assessed. Intravitreal aflibercept is already licensed and approved by the National Institute for Health and Care Excellence for use in DMO. This study shows that aflibercept can be safely added into our armamentarium for the management of PDR in the first year, allowing the use of one agent to tackle both sight threatening complications of diabetes mellitus in compliant patients. The robust randomised controlled trial design, high statistical power and excellent retention rates are particular strengths of this study. In addition, the study provides important evidence in the UK setting of a robust National Screening Programme. Those patients with not only high-risk PDR but any level of active PDR, whether previously treated or not, benefit at 1 year from this treatment with a superior visual outcome to that of standard PRP. This is the first study to show that anti-VEGF therapy is superior to PRP. It is therefore important that patients with PDR be informed of this therapy. However, patients need to be aware that close scrutiny of their eyes is required and, if left unmonitored and untreated, the condition can cause severe visual loss.

Trial registration

This trial is registered as ISRCTN32207582.

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