A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN)

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Scientific summary

The IVAN trial

Scientific summary

Introduction

Neovascular age-related macular degeneration (nAMD) is a bilateral condition causing severe central vision impairment. Ranibizumab (Lucentis®, Novartis), an antibody to vascular endothelial growth factor (VEGF), is an effective treatment. Bevacizumab (Avastin®, Roche), the parent molecule for ranibizumab, is licensed for other indications but not nAMD. It was identified as having similar benefits but at much lower cost. When the alternative treatments to the Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN) trial was conceived, there was no systematic review of VEGF inhibitors to treat nAMD, no head-to-head comparison of the two drugs and no data on minimum treatment frequency.

Objectives

The trial had three objectives. To estimate:

   i. the effectiveness of bevacizumab compared with ranibizumab
  ii. the effectiveness of discontinuous versus continuous treatment regimens, with criteria for restarting treatment when required in patients receiving discontinuous treatment
 iii. the cost-effectiveness of the alternative treatment strategies outlined above.

Methods

Study design
Multicentre, randomised, controlled factorial trial and within-trial economic evaluation, comparing the two drugs and two treatment regimens.

Settings and participants
Patients were recruited from UK NHS hospitals. Adults of ≥ 50 years of age, newly referred with nAMD in either eye, a best corrected distance visual acuity (BCVA) of ≥ 25 letters and a foveal neovascular lesion were eligible. Previous treatment for nAMD, fibrosis > 50% of the total lesion, greatest linear diameter of > 6000 μm, thick blood involving the centre of the fovea, other active ocular disease causing vision loss or ≥ 8 dioptres of myopia in the proposed study eye were exclusion criteria.

Interventions
Participants were allocated to one of four combinations: intravitreal injection of ranibizumab (0.5 mg) or bevacizumab (1.25 mg), and 'continuous' or 'discontinuous' treatment regimens. All participants attended monthly and were treated at visits 0, 1 and 2. Participants randomised to the continuous regimen were treated monthly thereafter; participants randomised to the discontinuous regimen were treated only if prespecified clinical and optical coherence tomography (OCT) criteria for active disease were met. If retreatment was initiated, three further doses at monthly intervals were mandated.

Randomisation
Randomisation was stratified by centre and blocked. Allocations were computer generated and concealed.

Masking
Investigators, outcome assessors and patients were masked to the drug throughout and to treatment regimen until visit 2 data were submitted.

Outcomes

The primary outcome was BCVA, assessed at baseline 3, 6, 12, 18 and 24 months. The primary end point was after 2 years of follow-up.

Secondary outcomes were:

(a) Contrast sensitivity, near visual acuity (NVA) and reading index.
(b) Lesion morphology [from colour fundus photography, fundus fluorescein angiography (FFA) and OCT].
(c) Two generic health status measures, European Quality of Life-5 Dimensions (EQ-5D) and Health Utilities Index version 3 (HUI3), and two macular-disease specific instruments: the MacDQoL (Macular disease Dependent Quality of Life: measuring the impact of macular disease on quality of life) and MacTSQ (Macular disease Treatment Satisfaction Questionnaire: measuring satisfaction with treatment for macular disease).
(d) Survival free from treatment failure.
(e) Resource use and quality-adjusted life-years (QALYs).
(f) Adverse events (AEs); the primary safety outcome was an arterial thrombotic event (ATE) or hospital admission for heart failure.
(g) Development of geographic atrophy (GA) during the trial.

Follow-up

Participants were followed monthly for 2 years. Colour photographs and OCTs were captured every 3 months, and FFA at baseline, 12 and 24 months. Participants completed the EQ-5D and HUI3 at visits 0, 3, 12 and 24, and when a serious adverse event (SAE) had occurred since the previous visit. MacDQoL and MacTSQ questionnaires were administered by telephone after visits 3, 12 and 24.

Sample size

We aimed to test non-inferiority hypotheses about visual function, with non-inferiority margins of 3 or 4 letters and analyses using one or two BCVA measurements, adjusted for baseline BCVA. Other assumptions were:

- no interaction between drug and treatment regimen
- BCVA standard deviation (SD) = 14 letters
- 90% power, 2.5% significance
- correlation between baseline and follow-up BCVA = 0.5, and between follow-up BCVA = 0.8.

For a 3-letter non-inferiority margin, 600 participants were required.

A prespecified interim analysis was undertaken after participants had been followed for 1 year.

Statistical analyses

Intention-to-treat analyses were carried out. Continuously scaled outcomes at multiple time points were analysed using linear mixed-effects methods. Binary outcomes were analysed using logistic regression, only if ≥ 10 participants experienced the outcome. Time to first treatment failure was analysed using Cox proportional hazards regression.

Effect estimates were reported separately by treatment regimen if the interaction of drug and treatment regimen reached statistical significance; otherwise, main effects of drug and treatment regimen were reported. No adjustment was made for multiple testing. Pre-planned subgroup analyses were tested by adding subgroup-by-treatment interactions. Fixed-effects meta-analyses combining the results of IVAN with other head-to-head trials were undertaken to place the trial findings within the context of existing evidence.

Economic evaluation

A within-trial economic evaluation was conducted to assess the incremental cost and cost-effectiveness of discontinuous and continuous treatment using bevacizumab and ranibizumab from the cost perspective of the NHS and the health perspective of participants. Health-care resource use was collected for all trial participants. The analysis included the cost of study medication; drug administration/monitoring consultations; any concomitant medication, ambulatory consultations and hospitalisations for 'related' AEs or SAEs. Costs and QALYs were discounted at 3.5% per annum.

Results

Patient screening

In total, 693 patients were screened: 65 excluded and 628 randomised.

Recruitment

Recruitment occurred between 27 March 2008 and 15 October 2010, with the last follow-up on 7 November 2012. Five of 628 randomised participants were subsequently found to be ineligible and 13 were not treated, leaving 610 who received at least one injection in the IVAN study cohort.

Withdrawals

Sixty participants withdrew. The most common reasons for withdrawal were illness preventing attendance and occurrence of a SAE.

Follow-up

In total, 525 of 610 participants completed the trial, with 87% of all scheduled visits attended. Missed visits were distributed similarly across groups.

Trial cohort

Mean age was 77.7 years (SD 7.4 years); 244 (40%) participants were male, 64% were current or past smokers and 19% had a history of dyspnoea. Characteristics were similar between groups, although more participants allocated to bevacizumab than ranibizumab had angina (17% vs. 11%).

Treatment received

The number of injections administered was similar by drug (ranibizumab: median 18; bevacizumab: median 19). More injections were given with continuous than discontinuous treatment (medians 23 vs. 13).

Success of masking

Ophthalmologists and participants reported not knowing which drug participants were receiving on > 97% of 3-, 12- and 24-month visits.

Unmasking

Unmasking was not required.

Primary outcome: best corrected distance visual acuity

Mean BCVA at 2 years was 67.8 and 66.1 letters in ranibizumab and bevacizumab groups and 66.6 and 67.3 letters in continuous and discontinuous groups. The difference between drugs (bevacizumab minus ranibizumab) was −1.37 letters [95% confidence interval (CI) −3.75 to +1.01 letters; $p = 0.26$] and between treatment regimens (discontinuous minus continuous) was −1.63 letters (95% CI −4.01 to +0.75 letters; $p = 0.18$). Bevacizumab was neither inferior nor non-inferior to ranibizumab, and discontinuous was neither inferior nor non-inferior to continuous treatment. There were no differences by subgroup for drugs or treatment regimens ($p \geq 0.26$).

A meta-analysis of changes in BCVA from baseline in seven trials showed that bevacizumab was statistically non-inferior to ranibizumab (–0.38 letters, 95% CI –1.47 to +0.70 letters; $p = 0.49$). Only CATT (Comparison of Age-related macular degeneration Treatment Trials) and IVAN compared treatment regimens; their combined data showed that discontinuous treatment was significantly inferior to continuous treatment (–2.23 letters, 95% CI –3.93 to –0.53 letters; $p = 0.010$).

Secondary measures of visual function at 2 years

Near visual acuity did not differ by drug [geometric mean ratio (GMR) = 0.94, 95% CI 0.85 to 1.04; $p = 0.23$] but was better with continuous treatment (GMR = 0.90, 95% CI 0.82 to 0.99; $p = 0.04$). Reading index was similar by drug and regimen. Contrast sensitivity did not differ significantly by drug, but was better with continuous treatment (mean difference = –1.07, 95% CI –1.90 to –0.25; $p = 0.011$).

Lesion morphology at 2 years

There were no significant differences by drug or treatment regimen for dye leakage on FFA but fewer participants treated with ranibizumab had fluid on OCT (50% vs. 59%; $p = 0.065$) and when treated continuously [45% vs. 63%, odds ratio (OR) = 0.47, 95% CI 0.33 to 0.67; $p < 0.001$].

Total thickness, and retinal plus subfoveal fluid thickness, at the fovea did not differ by drug. However, they were 9% and 8% less thick for continuous treatment (GMR = 0.91, 95% CI 0.85 to 0.97; $p = 0.004$; GMR = 0.92, 95% CI 0.84 to 1.00; $p = 0.046$, respectively).

A meta-analysis of changes in total retinal thickness at the fovea suggested a non-statistically significant difference in favour of ranibizumab ($p = 0.12$). The combined CATT and IVAN data showed a statistically significant difference in favour of continuous treatment ($p = 0.001$).

New GA during the trial developed in 30% of participants. There was no difference by drug (28% for ranibizumab vs. 31% for bevacizumab: OR = 0.87, 95% CI 0.61 to 1.25; $p = 0.46$) but GA developed significantly more often in the continuous group (34% vs. 26%, OR = 1.47, 95% CI 1.03 to 2.11; $p = 0.03$). This finding was confirmed in a meta-analysis (OR = 1.56, 95% CI 1.20 to 2.03; $p = 0.001$).

Adverse events

Overall, 171 participants had one or more SAEs, of whom 30 died. The primary safety end point frequency did not differ significantly by drug (OR = 1.69, 95% CI 0.80 to 3.57; $p = 0.16$) or regimen (OR = 0.56, 95% CI 0.27 to 1.19; $p = 0.13$). Deaths were split equally by drug but occurred more frequently in the discontinuous than continuous group (20 vs. 10, OR = 0.47, 95% CI 0.22 to 1.03; $p = 0.05$).

Gastrointestinal SAEs appeared to occur more frequently with bevacizumab. The percentages of patients having any systemic SAE were similar by drug (ranibizumab 26%, bevacizumab 27%) and treatment regimen (continuous 24%, discontinuous 29%); 39 non-ocular SAEs were classified as possibly, probably or definitely related to treatment.

Meta-analyses of safety outcomes showed no differences by drug for deaths or ATEs but a significantly increased risk of any systemic SAE for bevacizumab (OR = 0.77, 95% CI 0.64 to 0.92; $p = 0.004$). The comparison by treatment regimen showed increased risks of death (OR = 0.49, 95% CI 0.27 to 0.86; $p = 0.014$) and any systemic SAE (OR = 0.81, 95% CI 0.65 to 1.01; $p = 0.063$) with discontinuous treatment.

A post hoc meta-analysis of gastrointestinal SAEs showed a significantly increased risk of gastrointestinal SAEs in the bevacizumab group (OR = 0.53, 95% CI 0.33 to 0.85; $p = 0.009$) but no difference by treatment regimen (OR = 0.88, 95% CI 0.44 to 1.78; $p = 0.73$).

Patient-reported outcomes

The MacDQoL and MacTSQ scores and EQ-5D utilities were very similar at 1 and 2 years, both by drug and treatment regimen ($p \geq 0.23$).

Economic evaluation

All four groups accrued an average of 1.6 QALYs over 2 years, with no differences by drug or treatment regimen ($p \geq 0.381$). Total 2-year costs ranged from £3002 per patient (95% CI £2601 to £3403) for discontinuous bevacizumab to £18,590 per patient (95% CI £18,258 to £18,922) for continuous ranibizumab.

Ranibizumab was significantly more costly than bevacizumab ($p < 0.001$), costing an additional £14,989 per patient (95% CI £14,522 to £15,456) for continuous treatment and £8498 per patient (95% CI £7700 to £9295) for discontinuous treatment. As QALY differences were negligible, continuous ranibizumab cost £3.5M per QALY gained compared with continuous bevacizumab. Bootstrapping demonstrated that we can be > 99.99% confident that continuous ranibizumab is poor value for money compared with discontinuous ranibizumab at a £20,000 per QALY ceiling ratio.

Patients receiving continuous versus discontinuous bevacizumab accrued higher total costs (£599, 95% CI £91 to £1107; $p = 0.021$) but also accrued non-significantly more QALYs (mean difference: 0.020, 95% CI –0.032 to 0.071; $p = 0.452$). Continuous bevacizumab therefore cost £30,220 per QALY gained compared with discontinuous bevacizumab. However, this finding was substantially uncertain, with a 37% chance that continuous bevacizumab is cost-effective at a £20,000 per QALY ceiling ratio.

Discussion

Main findings: study results

Comparisons by drug and treatment regimen for BCVA were inconclusive. However, the BCVA meta-analysis showed that bevacizumab is non-inferior to ranibizumab and that discontinuous treatment is significantly inferior to continuous treatment. Secondary visual function and lesion morphology outcomes were consistent with the BCVA meta-analyses. New GA developed more often with continuous than discontinuous treatment.

Deaths and SAEs did not differ by drug. The meta-analyses of safety data by drug showed a significant increase in the risk of any systemic SAE, and SAEs classified as gastrointestinal, with bevacizumab. There were twice as many deaths in IVAN with discontinuous treatment, a finding confirmed in a meta-analysis. The odds of any systemic SAE by treatment regimen also tended to favour continuous treatment.

The economic evaluation demonstrated that ranibizumab is not cost-effective compared with bevacizumab. If hospitals in England were to switch from discontinuous ranibizumab to discontinuous bevacizumab, the NHS could save at least £102M per year [including 20% value added tax (VAT)]. Discontinuous bevacizumab is likely to be the most cost-effective treatment strategy evaluated in IVAN. However, this finding is substantially uncertain, with a 37% chance that continuous bevacizumab is cost-effective.

Strengths and limitations

The IVAN trial should directly inform the use of anti-VEGF drugs in the NHS. Secondary visual function outcomes supported the BCVA findings. Masking of the allocated drug and adherence to allocations of drug and treatment regimen were excellent. Retention of the elderly participants was good, with only 10% withdrawing. A detailed health-economic evaluation was carried out.

Potency, stability and sterility of bevacizumab in pre-filled syringes were tested using methods approved by the Medicines and Healthcare products Regulatory Agency. Our findings are generalisable only to bevacizumab sourced from manufacturing pharmacies with appropriate quality control processes.

Lessons for the future

Because the trial was considered to be 'high risk,' the IVAN trial design was modelled on commercial trials. To better understand outcomes in a clinical setting IVAN could have been more pragmatic; for example, we could have recruited both eyes, if both were eligible, and managed them according to same allocation.

In future, economic models to estimate the cost-effectiveness of interventions for nAMD should use robust associations between VA and utility estimated from large data sets using methods recommended by the National Institute for Health and Care Excellence. Our findings about the development of new GA highlight that these models may need to consider a long time horizon.

Combination therapies are being investigated with the aim of reducing treatment frequency. Our finding of possible risks of discontinuous treatment highlights the importance of careful monitoring of SAEs with such treatment regimens.

Conclusion

The IVAN trial and meta-analyses of data from other trials show that the choice of anti-VEGF treatment strategy is less straightforward than previously thought. Bevacizumab and ranibizumab have similar efficacy. Continuous treatment avoids the need to monitor disease activity on every visit, with slightly better functional outcomes. Our economic evaluation showed that ranibizumab represents poor value for money, discontinuous bevacizumab is probably better value for money than continuous bevacizumab, and monthly treatment with ranibizumab is unaffordable for publicly funded health systems.

Implications for health care

Findings from the IVAN trial:

- support using bevacizumab, which was non-inferior to ranibizumab, for both efficacy and safety
- highlight that economic models should use robust associations between VA and health-related quality of life, estimated from large data sets and adopting a long time horizon
- identify the need to monitor the frequency of SAEs with combination treatment regimens designed to reduce treatment frequency.

Recommendations for research

Research is needed to investigate:

- different models of service provision
- when treating nAMD may be futile
- the long-term consequences of anti-VEGF treatment
- reasons for poorer safety with discontinuous treatment.

Trial registration

This trial is registered as ISRCTN92166560.

Funding

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