Eplerenone versus placebo for chronic central serous chorioretinopathy: the VICI RCT

Andrew Lotery,[1]* Sobha Sivaprasad,[2] Abby O'Connell,[3] Rosie A Harris,[3] Lucy Culliford,[3] Angela Cree,[1] Savita Madhusudhan,[4] Helen Griffiths,[1] Lucy Ellis,[3] Usha Chakravarthy,[5] Tunde Peto,[5] Chris A Rogers[3] and Barnaby C Reeves[3]

[1]Department of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK
[2]NIHR Moorfields Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust, London, UK
[3]Bristol Trials Centre Clinical Trials and Evaluation Unit (BTC-CTEU), Bristol Royal Infirmary, University of Bristol, Bristol, UK
[4]Liverpool Ophthalmic Reading Centre, St. Paul's Eye Unit, Royal Liverpool University Hospitals NHS Trust, Liverpool, UK
[5]Centre for Vision Sciences, Queen's University Belfast, Belfast, UK

*Corresponding author a.j.lotery@soton.ac.uk

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Scientific summary

The VICI RCT

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Scientific summary

Introduction

Central serous chorioretinopathy is the fourth most common retinal disease. Each year, 10 in every 100,000 men and 2 in every 100,000 women in the population develop central serous chorioretinopathy. The condition is characterised by the build-up of subretinal fluid, which, when located subfoveally, results in central visual disturbance. Central serous chorioretinopathy is frequently bilateral, with most patients exhibiting signs of central serous chorioretinopathy in both eyes. In most patients, the first episode of central serous chorioretinopathy resolves spontaneously within 3 months. Persistence of subretinal fluid beyond 3 months is considered chronic and leads to permanent vision loss in up to one-third of patients.

Various treatments have been used despite limited high-quality evidence about their effectiveness. Photodynamic laser therapy with verteporfin is used in some cases; randomised controlled trials with half-dose photodynamic laser therapy have shown some encouraging results in the short term. However, verteporfin is not licensed for this indication and is expensive. Other laser treatments have been tried but have limited evidence of effectiveness and are not supported by trials.

Advances in retinal imaging show that eyes with central serous chorioretinopathy have a thickened choroid and dilated vessels. In addition, studies suggest that central serous chorioretinopathy is associated with choroidal hyperpermeability. Mineralocorticoid receptors have been implicated in the pathogenesis of central serous chorioretinopathy. Case series of central serous chorioretinopathy patients treated with oral mineralocorticoid receptor antagonists such as eplerenone, a specific mineralocorticoid receptor antagonist licensed for use in heart failure, and spironolactone, a non-specific mineralocorticoid receptor antagonist, have reported resolution of subretinal fluid and reduction of choroidal thickening as well as improvement in visual acuity in the short term. Despite a lack of robust clinical trial data, mineralocorticoid receptor antagonists are widely used by ophthalmologists as first-line therapy for treatment of central serous chorioretinopathy. Because these drugs can have serious systemic side effects, it is important to determine their efficacy and safety.

We carried out the first adequately powered randomised trial to determine whether or not eplerenone is safe and efficacious for treating central serous chorioretinopathy up to 12 months.

Objectives

The primary objective was to evaluate whether or not best corrected visual acuity following eplerenone treatment plus usual care is superior to placebo plus usual care in eyes with chronic central serous chorioretinopathy. Secondary objectives include evaluating whether or not eplerenone is better than placebo for a range of functional and morphological outcomes and evaluating safety over 12 months of follow-up.

Methods

Study design and participants

The VICI trial was a parallel, randomised, multicentre, double-masked, placebo-controlled superiority trial undertaken in 22 secondary care NHS hospitals in the UK. Patients with chronic central serous chorioretinopathy were screened in two stages: first, from their medical records and, second, after obtaining written informed consent, based on trial-specific assessments carried out to determine full eligibility.

In brief, patients aged 18–60 years with treatment-naive central serous chorioretinopathy of at least 4 months' duration were eligible. Patients were excluded if they had choroidal neovascularisation, any other disease that could affect visual acuity or cause retinal or subretinal fluid to accumulate, > −6 dioptres of myopia, or hyperkalaemia (blood serum potassium level of > 5.0 mmol/l).

The trial was sponsored by the University Hospital Southampton NHS Trust and approved by the Wales Research Ethics Committee (16/WA/0069) and the Medicines and Healthcare products Regulatory Agency (EudraCT2016-000113-70).

Randomisation and masking

Participants were randomly allocated (1 : 1) to eplerenone plus usual care or placebo plus usual care. Usual care was administered at the clinician's discretion. Randomisation was blocked (block sizes of two and four) and stratified by hospital and visual acuity [Early Treatment Diabetic Retinopathy Study chart scores of 54–67 letters (low visual acuity) or 68–85 letters (high visual acuity)]. The allocation list was generated by the trial statistician using Stata® version 14.0 (StataCorp LP, College Station, TX, USA) before starting recruitment and supplied to the production unit responsible for overencapsulating eplerenone tablets and manufacturing identical placebo capsules. Participants, clinical teams, outcome assessors, hospital pharmacists and the trial management group were masked to participants' allocations.

Randomisation was performed by ophthalmologists or research nurses within 4 weeks of screening via a secure internet-based randomisation system.

Procedures

Participants were prescribed 25 mg/day of oral eplerenone or placebo for the first week, which increased to 50 mg/day for up to 12 months providing that the participant's blood serum potassium level was ≤ 5.0 mmol/l. Participants were followed up at 1 week, 4 weeks and 3, 6, 9 and 12 months. Participants were classified as 'adherent' if they took > 70% of the prescribed capsules between follow-up visits. Participants ceased the study drug if subretinal fluid had completely resolved at any follow-up visit and restarted the study drug if subretinal fluid recurred at a subsequent follow-up visit, following the same dose escalation procedure. If a participant's serum potassium level exceeded 5.0 mmol/l at any follow-up visit, the study drug was stopped permanently and the participant was invited to continue to be followed up during the 12-month follow-up period.

Outcomes

The primary outcome was best corrected visual acuity score at 12 months as measured by Early Treatment Diabetic Retinopathy Study charts. Best corrected visual acuity was measured at all follow-up visits, excluding at week 1, by masked, trial-accredited optometrists.

Secondary outcomes were low-luminance visual acuity; central subfield retinal thickness; change in subretinal fluid thickness from baseline; systemic and ocular adverse events; macular atrophy of the retinal pigment epithelium; subfoveal choroidal thickness; choroidal permeability; time to resolution of subretinal fluid; classification of subretinal fluid resolution as complete, partial or none; classification of subretinal fluid resolution as early, late or none; time to recurrence of subretinal fluid; fundus fluorescein angiography phenotype; incidence of central serous chorioretinopathy in the fellow eye; and patient-reported visual function. Retinal images were graded by masked, accredited graders in the Network of Ophthalmic Reading Centres UK.

Adverse events

Adverse events and reactions were recorded throughout the 12-month follow-up period. Events were coded using Medical Dictionary for Regulatory Activities (version 14.1) categories.

Statistical analysis

A target sample size of 104 patients was chosen for the trial to have 90% power to detect a difference of ≥ 5 letters at a 5% significance level (two-tailed) given an anticipated drop-out rate of $< 15\%$ during follow-up. The assumptions underpinning this calculation have been described elsewhere (Willcox A, Culliford L, Ellis L, Rogers CA, Cree A, Chakravarthy U, *et al.* Clinical efficacy of eplerenone versus placebo for central serous chorioretinopathy: study protocol for the VICI randomised controlled trial. *Eye* 2019;**33**:295–303).

Analyses were directed by a prespecified statistical analysis plan and performed on a modified intention-to-treat basis. The only patients excluded were those who withdrew and were unwilling for data already collected to be analysed or who had attended no post-randomisation visit at which the primary outcome was measured. Continuous data are summarised using mean and standard deviation (or median and interquartile range if distributions were skewed) and categorical data as number and percentage. Outcomes were compared using linear regression (continuous outcomes), proportional hazards parametric survival models for interval-censored data (time-to-event outcomes) or mixed-effects regression (continuous longitudinal outcomes). All analyses used placebo with usual care as the reference group and were adjusted for stratification factors where possible. Results are reported as effect estimates with 95% confidence intervals. A prespecified exploratory analysis was performed to assess the effect of adherence and treatment on the primary outcome. Sensitivity analyses (1) adjusting time-to-event outcomes for baseline imbalances in prognostic factors and (2) reassessing the effect of adherence and treatment on the primary outcome after imputing pill counts for lost bottles were performed. Two post hoc analyses (1) re-estimated the treatment effects for best corrected visual acuity, central subfield retinal thickness, subretinal fluid thickness and choroidal thickness after adjusting for photodynamic laser therapy administered during follow-up and (2) analysed choroidal thickness in the fellow eye. All analyses were performed in Stata version 15.1.

The trial was overseen by an independent Data Monitoring and Steering Committee that reported their recommendations to an independent Trial Steering Committee.

Results

A total of 114 participants were randomised between 11 January 2017 and 22 February 2018: 57 to the eplerenone group and 57 to the placebo group. A total of 402 patients were screened for inclusion and 305 were initially eligible; 223 were approached and 179 consented to participate but 64 were subsequently found to be ineligible and one patient withdrew consent.

A total of 111 participants consented for their data to be analysed and attended at least one post-randomisation visit at which the primary outcome was measured. Adherence was similar between groups. There were few protocol deviations, excluding visits attended too early or too late.

Participant characteristics were similar between the two groups. Some participants did not take capsules throughout follow-up, either because central serous chorioretinopathy resolved completely or because they had an adverse event. There was no apparent difference between groups in the proportion of time they were taking capsules.

The modelled mean best corrected visual acuity score at 12 months was 80.4 letters (standard deviation 4.6 letters) in the eplerenone group and 79.5 letters (standard deviation 4.5 letters) in the placebo group. On average, best corrected visual acuity score increased by about four letters in both groups over the 12-month follow-up period. There was no difference in best corrected visual acuity score at 12 months between the groups (mean difference 1.73 letters, 95% confidence interval −1.12 to 4.57 letters; $p = 0.51$). The exploratory analysis found no effect of adherence and treatment on best corrected visual acuity score irrespective of whether or not pill counts were imputed for lost

investigational medicinal product bottles. The post hoc analysis of best corrected visual acuity, adjusting for photodynamic therapy administered during follow-up, did not change the findings.

There were no apparent differences between the groups for the pattern of complete resolution of subretinal fluid or recurrence of central serous chorioretinopathy, with or without adjustment for baseline subretinal fluid thickness. Central subfield retinal thickness at 12 months did not differ between groups (mean difference 24.35 µm, 95% confidence interval −7.86 to 56.56 µm; $p = 0.14$) but there was a statistically significant difference in subretinal fluid thickness favouring placebo at 12 months post randomisation (mean difference 48.08 µm, 95% confidence interval −13.34 to 82.73 µm; $p = 0.007$).

Serum potassium levels were very similar in both groups during follow-up; levels of > 5.0 mmol/l triggered discontinuation of the investigational medicinal product in eight participants in each group (14%). There were three serious adverse events; none was considered related to the investigational medicinal product and all occurred in participants in the placebo group.

Discussion

Main findings: study results

The VICI trial has shown that eplerenone did not result in an improvement of best corrected visual acuity score by ≥ 5 letters compared with placebo over a 12-month period. None of the secondary outcomes suggested a benefit of eplerenone. Unexpectedly, subretinal fluid thickness and choroidal thickness significantly favoured placebo. We have no definitive explanation for these significant findings. The treatment effects for best corrected visual acuity, time-to-event outcomes and key morphological outcomes were unaltered in additional sensitivity, exploratory and post hoc analyses. The failure to find a difference cannot be attributed to limitations of the trial: the primary analysis included data for 97% of randomised participants, participants attended 94% of all scheduled visits and there were no protocol deviations affecting the treatment comparison.

Qualitatively, profiles of sodium levels during follow-up were very similar between the two groups and an equal number of patients had hyperkalaemia (an expected adverse event) in each group (based on the prespecified threshold). The low frequencies of other complications precluded formal comparisons between groups.

We found no evidence of benefit or harm of eplerenone other than the differences between groups in subretinal fluid thickness and choroidal thickness that favoured placebo.

Strengths and limitations

The strengths of the trial were as follows: all but three participants contributed to the primary analysis, power was increased by participants attending almost all scheduled visits and there were no compromising protocol deviations.

Limitations included discontinuing treatment if central serous chorioretinopathy resolved during follow-up or hyperkalaemia occurred, which may have reduced the observed treatment effect. With hindsight we should have adopted a higher treatment cessation threshold, such as that for the licensed indication for eplerenone. Our inability to control the use of co-treatments was a limitation that could have introduced bias if used differentially by group. Photodynamic laser therapy was administered to slightly more participants in the placebo group but post hoc analysis found that this did not affect the primary analysis.

Regarding generalisability, although some patients were excluded because their best corrected visual acuity score was too good, we have no reason to believe that the effects of eplerenone in these

patients would have been any different. In other respects, the characteristics of the trial participants were similar to the wider central serous chorioretinopathy population.

Our eligibility criteria combined with multiple imaging modalities at screening prevented the inclusion of patients with conditions that can be phenotypically similar to central serous chorioretinopathy to avoid dilution of the cohort.

Lessons for the future

With regards to the investigational medicinal product manufacture, we learned that it is important to obtain multiple quotes from different pharmacies and to seek expert input on what to look out for in such quotes. In addition, we recommend budgeting for more investigational medicinal product than required to avoid moving stock from low- to high-recruiting sites and to be able to cover all eventualities, such as more patients having disease recurrence than expected. Some of the issues we experienced were due to nuances of this trial design; however, planning for more stock than needed is likely to reduce subsequent logistical issues in many trials. In addition, we learned to stagger the manufacture of batches such that the first batch is small to reduce the risk of stock expiring in the event of recruitment delays.

There is also a lesson for future trials on treatments for central serous chorioretinopathy relating to visual acuity. Because presenting visual acuity in eyes with central serous chorioretinopathy can be improved by refraction, this raises the question of how a visual acuity eligibility criterion should be defined. Because visual acuity does not reflect the visual problems that patients experience, it raises the question of whether or not visual acuity should be the primary outcome in central serous chorioretinopathy trials. There needs to be a discussion involving all stakeholders about the pros and cons of choosing other measures, such as retinal fluid or microperimetry, as a primary outcome.

The disadvantage of not using visual acuity as an eligibility criterion or as the primary outcome is the difficulty in putting central serous chorioretinopathy in context alongside other visually disabling conditions. Microperimetry may be a better end point for future clinical trials; however, microperimetry is not used routinely in clinical practice and, therefore, it is not widely available. A future study correlating structural changes (e.g. subretinal fluid) with microperimetry would be useful; if these were strongly correlated, then presence of subretinal fluid could be considered as a trial end point because subretinal fluid is easily measured with readily available optical coherence tomography equipment.

Conclusion

In summary, the VICI trial had many strengths, with no obvious areas for introducing bias. We found no evidence of a clinically important benefit of eplerenone for the treatment of central serous chorioretinopathy. The trial results should prompt ophthalmologists to review the use of eplerenone for treating central serous chorioretinopathy and to participate in future trials of other potential interventions.

Trial registration

The trial is registered as ISRCTN92746680.

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