

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

Sobha Sivaprasad,^{1,2*} Philip Hykin,¹ A Toby Prevost,³
Joana Vasconcelos,³ Amy Riddell,⁴ Jayashree Ramu,¹
Caroline Murphy,⁴ Joanna Kelly,⁴
Rhiannon Tudor Edwards,⁵ Seow Tien Yeo,⁵
James Bainbridge,² David Hopkins⁶
and Beverley White-Alao⁴

¹National Institute for Health Research Clinical Research Facility, Moorfields Biomedical Research Centre, London, UK

²University College London Institute of Ophthalmology, London, UK

³Imperial Clinical Trials Unit, School of Public Health, Imperial College London, London, UK

⁴King's Clinical Trials Unit King's College London, London, UK

⁵Centre for Health Economics and Medicines Evaluation, Bangor University, Bangor, UK

⁶Department of Diabetes and Endocrinology, King's College Hospital NHS Foundation Trust, London, UK

*Corresponding author Sobha.sivaprasad@ Moorfields.nhs.uk

Declared competing interests of authors: Sobha Sivaprasad reports grants and non-financial support from Bayer HealthCare, Bayer Plc (Reading, UK) during the conduct of the study and has received research grants, travel fees and advisory board honoraria from Bayer HealthCare, Novartis Pharmaceuticals UK Ltd (Frimley, UK), Allergan Ltd (Marlow, UK) and Roche Holding AG (Basel, Switzerland); grants and advisory board honoraria from Boehringer Ingelheim (Ingelheim am Rhein, Germany); and advisory board honoraria from Heidelberg Engineering GmbH (Heidelberg, Germany), outside the submitted work. Philip Hykin reports grants, personal fees and non-financial support from Bayer HealthCare during the conduct of the study.

Published October 2018

DOI: 10.3310/eme05050

Plain English summary

The CLARITY non-inferiority RCT

Efficacy and Mechanism Evaluation 2018; Vol. 5: No. 5

DOI: 10.3310/eme05050

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Plain English summary

Diabetes mellitus causes small blood vessels in the eye to close, starving the retina of oxygen. To attempt to repair the situation, the retina produces a protein, vascular endothelial growth factor (VEGF), that promotes the growth of new blood vessels. These new blood vessels have a high risk of bleeding and can pull the retina, causing retinal detachment. This stage of diabetic eye disease is called proliferative diabetic retinopathy (PDR) and can result in severe loss of eyesight. The current standard of care for this condition is panretinal photocoagulation (PRP), which involves destroying the retina that is starved of oxygen with a laser so that the demand for oxygen is reduced, which will in turn cause the retinal vessels to shrink, disappear or stop growing. However, the destruction of the retina with a laser is associated with adverse events on visual function. Therefore, better treatment approaches are required for this condition. Injections of anti-VEGF agents into the eye are routinely used in people with diabetes mellitus who suffer from diabetic macular oedema. In this study, we tested whether or not aflibercept, the most recently licensed anti-VEGF agent, could be used as an alternative to PRP for PDR.

We randomly allocated 232 participants from 22 NHS hospitals to receive either intravitreal aflibercept injections or PRP and compared the clinical effectiveness and cost-effectiveness outcomes.

From a public sector multiagency perspective that covers health and social care services, at an increased cost, participants treated with aflibercept had better outcomes for PRP in terms of visual acuity, more frequent regression of new vessels and fewer complications. As the study was only for 52 weeks, there is uncertainty about the need for further aflibercept in subsequent years. Long-term studies are required to understand the outcomes and cost implications of treating patients with anti-VEGF treatment for this condition for many years.

Headlines

Intravitreal aflibercept injections provided superior visual acuity and other positive clinical outcomes at 52 weeks compared with PRP in patients with PDR. If society is willing to pay £1400 for an additional 1-point improvement in best corrected visual acuity, then aflibercept has a 56.6% probability of being cost-effective at the list price of £816. From 20% through to 100% Patient Access Scheme, results showed 100% probability of aflibercept being cost-effective at the hypothetical societal willingness-to-pay threshold of £1400.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full EME archive is freely available to view online at www.journalslibrary.nihr.ac.uk/eme. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Efficacy and Mechanism Evaluation* journal

Reports are published in *Efficacy and Mechanism Evaluation* (EME) if (1) they have resulted from work for the EME programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

EME programme

The Efficacy and Mechanism Evaluation (EME) programme was set up in 2008 as part of the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) coordinated strategy for clinical trials. The EME programme is broadly aimed at supporting 'science driven' studies with an expectation of substantial health gain and aims to support excellent clinical science with an ultimate view to improving health or patient care.

Its remit includes evaluations of new treatments, including therapeutics (small molecule and biologic), psychological interventions, public health, diagnostics and medical devices. Treatments or interventions intended to prevent disease are also included.

The EME programme supports laboratory based or similar studies that are embedded within the main study if relevant to the remit of the EME programme. Studies that use validated surrogate markers as indicators of health outcome are also considered.

For more information about the EME programme please visit the website: <http://www.nets.nihr.ac.uk/programmes/eme>

This report

The research reported in this issue of the journal was funded by the EME programme as project number 12/66/15. The contractual start date was in July 2014. The final report began editorial review in July 2017 and was accepted for publication in March 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the MRC, NETSCC, the EME programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the EME programme or the Department of Health and Social Care.

© Queen's Printer and Controller of HMSO 2018. This work was produced by Sivaprasad *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

NIHR Journals Library Editor-in-Chief

Professor Tom Walley Director, NIHR Evaluation, Trials and Studies and Director of the EME Programme, UK

NIHR Journals Library Editors

Professor Ken Stein Chair of HTA and EME Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

Professor Andrée Le May Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals)

Dr Martin Ashton-Key Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

Professor Matthias Beck Professor of Management, Cork University Business School, Department of Management and Marketing, University College Cork, Ireland

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin Senior Scientific Advisor, Wessex Institute, UK

Dr Peter Davidson Director of the NIHR Dissemination Centre, University of Southampton, UK

Ms Tara Lamont Scientific Advisor, NETSCC, UK

Dr Catriona McDaid Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Professor of Wellbeing Research, University of Winchester, UK

Professor John Norrie Chair in Medical Statistics, University of Edinburgh, UK

Professor John Powell Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

Professor James Raftery Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, UCL Great Ormond Street Institute of Child Health, UK

Professor Jonathan Ross Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Jim Thornton Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Professor Martin Underwood Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK

Please visit the website for a list of editors: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk