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A Crossover Design for Comparative Efficacy

A 36-Week Randomized Trial of Bevacizumab and Ranibizumab for Diabetic Macular Edema

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Purpose: To investigate the comparative efficacy of bevacizumab (Avastin) and ranibizumab (Lucentis; both Genentech, Inc, South San Francisco, CA) for diabetic macular edema (DME) using a crossover study design.

Design: Randomized, double-masked, 36-week, 3-period crossover clinical trial.

Participants: Fifty-six subjects with DME involving the center of the macula in one or both eyes.

Methods: Monthly intravitreous injections of bevacizumab (1.25 mg) or ranibizumab (0.3 mg).

Main Outcome Measures: Comparison of mean changes in visual acuity and central retinal thickness, tested using a linear mixed-effects model.

Results: Based on the linear mixed-effects model, the 3-month estimated mean improvement in visual acuity was 5.3 letters for bevacizumab and 6.6 letters for ranibizumab (difference, 1.3 letters; $P = 0.039$). Estimated change in optical coherence tomography (OCT) central subfield mean thickness (CSMT) was −89 μm for bevacizumab and −137 μm for ranibizumab (difference, 48 μm; $P < 0.001$). Incorporating cumulative treatment benefit, the model yielded a predicted 36-week (9-month) average improvement in visual acuity of 7.1 letters (95% confidence interval [CI], 5.0−9.2) for bevacizumab and 8.4 letters (95% CI, 6.3−10.5) for ranibizumab, and a change in OCT CSMT of −128 μm (95% CI, −155 to −100) for bevacizumab and −176 μm (95% CI, −202 to −149) for ranibizumab. There was no significant treatment-by-period interaction (i.e., treatment difference was constant in all 3 periods), nor was there a significant differential carryover effect from one period to the next.

Conclusions: This trial demonstrated a statistically significant but small relative clinical benefit of ranibizumab compared with bevacizumab for treatment of DME, using a markedly reduced sample size relative to a full comparative efficacy study. The effects on visual acuity and central retinal thickness for the 2 drugs are consistent with those reported at 1 year for the concurrent parallel-group trial by the Diabetic Retinopathy Clinical Research Network testing bevacizumab, ranibizumab, and aflibercept for DME. The 3-period crossover design allowed for meaningful and efficient comparison, suggesting that this approach may be useful for future comparative efficacy studies of anti−vascular endothelial growth factor drugs for DME. *Ophthalmology 2016;■:1−9 © 2016 Published by Elsevier on behalf of the American Academy of Ophthalmology.*

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The comparative efficacy of bevacizumab (Avastin; Genentech, Inc, South San Francisco, CA), ranibizumab (Lucentis; Genentech), and aflibercept (Eylea, Regeneron Pharmaceuticals, Inc, Tarrytown, NY) for treatment of diabetic macular edema (DME) is being investigated in a large, randomized, parallel-group clinical trial carried out by the Diabetic Retinopathy Clinical Research Network (DRCR.net; ClinicalTrials.gov identifier, NCT01627249). Recently reported 1-year results for this study demonstrate efficacy for all 3 drugs.[1] Analysis of the primary outcome, mean change in visual acuity at 1 year, showed that there was an overall relative benefit of aflibercept compared with the other 2 drugs. However, there was a statistically significant interaction between baseline visual acuity and the treatment effect for aflibercept, warranting stratification of the results by baseline visual acuity. The treatment effect was similar among the 3 drugs for eyes with baseline visual acuity score of 69 letters or more (Snellen equivalent, approximately 20/40 or better) and demonstrated superiority of aflibercept for eyes with a baseline visual acuity score of fewer than 69 letters (Snellen equivalent, worse than 20/40).

Ranibizumab (0.3 mg) and aflibercept (2 mg) are approved by the United States Food and Drug Administration (FDA) for the treatment of DME, based on results of several randomized clinical trials.[2−5] Bevacizumab has not

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been tested for this indication in a large clinical trial before the DRCR.net study, but has been used widely off-label in recent years on the basis of benefit shown in case series and small trials,[6–11] and has shown efficacy equal to that of ranibizumab in large clinical trials for neovascular age-related macular degeneration.[12–17]

The findings of the DRCR.net trial offer invaluable and definitive guidance about the comparative efficacy of available anti–vascular endothelial growth factor (VEGF) agents for treatment of DME. Such studies are the gold standard for comparative efficacy research, but the investment necessary to execute these projects is large, and the time necessary to organize and carry out these trials is considerable.

We asked whether a crossover study design might offer a meaningful and efficient comparison of 2 intravitreally administered anti-VEGF drugs for DME, using a smaller sample size than required for a traditional parallel-group trial. We specifically wanted to compare findings from a small crossover study with those from the large comparative efficacy trial being planned by the DRCR.net. Crossover studies, in which every participant receives both treatments being compared, offer statistical efficiency that permits use of a smaller sample size than would be required for a parallel-group trial, in which each participant receives only 1 treatment being tested. Some crossover trial designs can be problematic, particularly when carryover effects (residual effects) of one drug complicate measurement of the effects of a second drug in subjects given one and then the other, making it difficult or impossible to evaluate a treatment difference. Two-period, 2-sequence designs susceptible to such problems have been criticized and are used infrequently in biomedical research.[18] However, extended crossover designs making use of additional treatment periods and sequences have been developed to overcome these shortcomings under appropriate conditions.[19,20]

The treatment effect of anti-VEGF drugs on DME, which is rapid, easily measured, and typically reversible in the short term, combined with the similarities of the drugs, seemed well suited to this design. We chose to compare bevacizumab and ranibizumab, the 2 anti-VEGF drugs most widely used for treatment of DME at the time of study initiation, and carried out this trial concurrently with the DRCR.net study to compare findings from the 2 study designs.

Methods

This randomized, double-masked, 36-week, 3-period, 2-treatment crossover clinical trial was conducted at 2 sites, the National Eye Institute, Bethesda, Maryland, and University Hospitals Bristol National Health Service Foundation Trust, Bristol, United Kingdom, with the Emmes Corporation, Rockville, Maryland, acting as the Data and Statistical Coordinating Center. Institutional review board or independent ethics committee approval was obtained at both sites, and all participants gave written informed consent. The study was conducted in accordance with the tenets of the Declaration of Helsinki. No stipend was given for participation. An independent data and safety monitoring committee provided study oversight and approved this manuscript. The study is registered at www.clinicaltrials.gov under identifier NCT01610557. This project was supported with federal funds from the National Eye Institute, National Institutes of Health, Department of Health and Human Services, under contract no. HHSN263201200001C. Patient recruitment and clinical research staff costs also were supported in the United Kingdom by the National Institute for Health Research's Clinical Research Network West of England and Moorfields Biomedical Research Center, as part of the Universities and National Institutes Transatlantic Eye consortium (UNITE).

Study Population

Eligible participants had type 1 or type 2 diabetes mellitus, were at least 18 years of age, and could enter one or both eligible eyes in the study. Principal eligibility criteria for a study eye included: (1) presence of DME involving the center of the macula, (2) Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity letter score of 78 to 24 (Snellen equivalent, 20/32–20/400), and (3) central subfield mean thickness (CSMT) of 330 μm or more on Cirrus (Carl Zeiss Meditec, Inc, Dublin, CA) optical coherence tomography (OCT). Major exclusion criteria for the study eye included presence of factors or other conditions judged to impact the course of edema or to preclude possible improvement in vision with treatment; panretinal photocoagulation, focal or grid laser photocoagulation, or depot corticosteroid injection within the previous 3 months; ocular injection with an anti-VEGF agent within the previous 2 months; more than 4 injections with an anti-VEGF agent within the previous year; or prior vitrectomy. Potential participants were excluded for history of renal failure (requiring hemodialysis or renal transplantation) and for a measured systolic blood pressure of more than 180 mmHg or a diastolic blood pressure of more than 110 mmHg.

Study Design

This study used a randomized, double-masked, 3-period, 2-treatment crossover design with 4 treatment sequence patterns. Each of 3 12-week periods consisted of 3 intravitreous injections of ranibizumab (0.3 mg) or bevacizumab (1.25 mg), given every 4 weeks, with evaluation of the treatment period 4 weeks after the third dose (i.e., weeks 12, 24, and 36).

Each study eye received 9 monthly injections over the course of the trial, according to a pattern of treatments determined by 1 of 4 randomly assigned sequences: R-R-B, R-B-B, B-B-R, or B-R-R, where R indicates a series of 3 consecutive ranibizumab injections, and B represents a series of 3 consecutive bevacizumab injections. Participants were assigned to 1 of the 4 treatment sequences using a randomization list generated by the Data and Statistical Coordinating Center before study initiation, with balance after every 12 enrollments. The list was provided to unmasked pharmacists at each site, who confirmed a valid participant identification code before dispensing study treatment. Both clinical sites used the same randomized list, but selected treatment assignments from opposite ends. For participants entering both eyes in the trial, the right eye was assigned randomly as above to 1 of the 4 treatment sequences, and the left eye was assigned automatically to the sequence with the inverse schedule (for example, B-R-R in the right eye and R-B-B in the left eye).

Treatment

Participants and investigators were masked to treatment. Site staff collecting study data, including research coordinators, technicians, and photographers, were also masked. Bevacizumab (1.25 mg) or ranibizumab (0.3 mg) was administered every 4 weeks according to a study eye's randomly assigned schedule. Visits were scheduled