2RT PAPER SUMMARY

Pilot randomised trial of a nanopulse retinal laser versus conventional photocoagulation for the treatment of diabetic macular oedema

Aim: Assess the efficacy of new nanopulse laser in the treatment of diabetic macular oedema. A randomised, non-inferiority trial.

Summary Outcome: In the short term 2RT laser approximates the clinical efficacy of conventional thermal photocoagulation. The difference in retinal thickness between the two groups was 5.6mm in favour of the 2RT, secondary outcome of change in VA of 0.02 in favour of the 2RT. No observable adverse events reported.

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Original Article

Pilot randomized trial of a nanopulse retinal laser versus conventional photocoagulation for the treatment of diabetic macular oedema

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Abstract

Background: To assess the efficacy of a new nanopulse laser, retinal regeneration therapy for the treatment of diabetic macular oedema.

Design: Randomized, non-inferiority, trial.

Participants: 20 eyes of 17 subjects in the retinal regeneration therapy group and 18 eyes of 14 subjects in the conventional group were analysed.

Methods: The treatment group received retinal regeneration therapy laser, and the control group received photocoagulation.

Main Outcome Measures: The primary outcome was the optical coherence tomography-measured change in central retinal thickness at 6 months. A secondary outcome was the change in logarithm of minimum angle of resolution visual acuity at 6 months. Non-inferiority required the one-sided 95% confidence interval of the mean retinal thickness reduction after retinal regeneration therapy to be within 35 μm of the reduction after control laser.

Results: When outliers were included in the dataset, the difference in retinal thickness reduction by analysis of covariance was 10.9 (standard deviation 17.6) mm in favour of the control laser. The difference between groups in retinal thickness reduction was 40.8 mm. If two extreme outliers were excluded, the difference was 5.6 (standard deviation 14.2) mm in favour of the retinal regeneration therapy laser, and the D optical coherence tomography was 18.5 mm. The visual acuity difference between groups was 0.059, meeting non-inferiority requirements.

Conclusions: Although retinal thickness reduction was not unambiguously non-inferior, in the short-term, retinal regeneration therapy approximates the clinical efficacy of conventional photocoagulation, stabilizing visual acuity and providing motivation for larger trials assessing retinal regeneration therapy.

Key words: diabetic retinopathy photocoagulation, laser surgery, macular.

Introduction

A quarter of a century ago, the Early Treatment Diabetic Retinopathy Study (ETDRS) provided convincing evidence that laser photocoagulation reduced the rate of visual acuity (VA) reduction from diabetic macular oedema (DMO).[1] Photocoagulative laser remains the standard treatment for DMO, but its mechanism of action remains unclear. Possible mechanisms include a reduction in capillary permeability or an increase in active transport of fluid from retina to blood.[2,3] Given that the mechanism is

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unclear, it is plausible that photocoagulation *per se* is not necessary for effective treatment. Furthermore, standard photocoagulation produces a thermal injury to the lasered tissue, compromising its safety profile. Photocoagulation for the treatment of DMO can cause collateral damage to the overlying sensory retina, subretinal fibrosis and enlargement of burns with time, complications that are energy dependent and can have devastating visual results.[4–6] Hence, an alternative laser treatment that was at least as effective and potentially safer would be clinically desirable.

These factors motivated the development of a new nanopulse laser, retinal regeneration therapy (2RT; Ellex R&D Pty Ltd, Adelaide, Australia), which delivers approximately 0.2% of the energy per pulse compared with standard photocoagulation. The design of the 2RT laser also includes a unique beam profile that finely distributes the delivered energy over the treatment spot so that treatment effects can be completely confined within the retinal pigment epithelium. Histological examination of retinas from lasered animals demonstrated remarkably little or no destructive injury to the overlying photoreceptor layer at clinically relevant energy settings. (Chidlow G, unpublished data, 2011) An interventional case series of 2RT for the treatment of DMO conducted in London, U.K. (unpublished data) was not associated with any adverse events and suggested that further data regarding its efficacy was worth pursuing.

Our primary hypothesis was that 2RT was at least as effective as conventional photocoagulation for the treatment of DMO in reducing retinal thickening as measured by optical coherence tomography (OCT). A secondary hypothesis was that 2RT was at least as effective as conventional photocoagulation for the treatment of DMO in preserving VA. Herein, we report the results of a pilot, phase II, randomized, non-inferiority trial of 2RT versus conventional photocoagulation for the treatment of DMO. Given the potentially better safety profile of the new laser with minimal tissue destruction compared with photocoagulation, the rationale for the study was that results, which supported the hypothesis, would provide motivation to proceed to a larger randomized trial.

Methods

Design

This was a randomized, non-inferiority, parallel-group study conducted in Australia (at two sites). Methodology was modelled on a recent Diabetic Retinopathy Clinical Research Network Trial study[7] and was guided by the Consolidated Standards of Reporting Trials 2010 update.[8]

Ethics and clinical trial registration

Ethics committee approval was obtained, and the study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12608000369325).

Eligibility and allocation

Patients were recruited from two retinal clinics. To be eligible, subjects had to be at least 18 years of age and have types 1 or 2 diabetes mellitus, with one or both of their eyes meeting the following criteria: (i) a best-corrected ETDRS VA score of 19 or more letters; (ii) a retinal thickness measured on Stratus 3.0 OCT (Carl Zeiss Meditec, Dublin, CA, USA) of 250 μm or more in the central subfield, or 300 μm or more in at least one of the four inner subfields; and (iii) no prior laser treatment or other treatment for DMO. Eyes were not eligible if they had retinal thickening from any other cause or had undergone any ocular surgery within the prior 6 months.

Eyes were randomized to either 2RT or the control group using a simple randomization process without blocking or stratification. The trial coordinator performed the randomization procedure and retained sequentially numbered opaque containers that were opened by the treating clinicians just prior to laser.

VA testing and OCT measurements were performed by masked observers. After the initial laser treatment, the patient was seen at a 3-month follow-up visit, and a further laser treatment was applied at the clinicians' discretion.

Treatment protocols

The 2RT laser produces single pulses of 3-ns duration at a wavelength of 532 nm, with a delivered beam profile that finely distributes the energy over the treatment spot. The photocoagulator laser was an Integre (Ellex Medical Lasers Ltd, Adelaide, Australia) providing variable length pulses at a wavelength of 532 nm, with a 'top hat' beam profile. The two treatment techniques differed in the following aspects: 2RT applications were delivered with a spot size of 400 μm at an energy setting that produced nil reaction or a barely discernible retinal reaction (approximately 0.3 mJ) with each application (the current 2RT laser has a fixed 400-μm spot size). The 2RT laser energy was first titrated up to the point of the first visible reaction, which appeared as subtle retinal blanching. Slightly lower energy was then selected for treatment. This method provided individual compensation for variations in corneal, lens or vitreous opacities, and also retinal pigmenta-

tion variations. The titration of the laser energy was applied to non-thickened regions outside the macula. As the applications were advanced to thickened retinal regions, there was generally no observable reaction. 2RT laser was applied in a grid pattern, one 'burn' width apart to thickened areas of retina at least 500 μm from the foveal centre, with a range of approximately 20–120 applications. Microaneurysms were not directly treated. The same parameters were used for re-treatment if necessary. The ETDRS direct/grid photocoagulation involved treating only areas of thickened retina and directly treating leaking microaneurysms with light burns, a spot size of 100 ìm and typical pulse durations of 0.1 s.

Data collection

At baseline and each follow-up visit, best-corrected VA in each eye was recorded using an ETDRS chart. A fluorescein angiogram (FFA) was obtained, and central retinal thickness (CRT) was recorded using the Stratus OCT 3.0 (Carl Zeiss Meditec, Dublin, CA, USA). Blood pressure recordings and haemoglobin A1c measurements were also taken at each visit. Data were entered into an electronic spreadsheet by trained personnel. Data from the OCT central subfield and four inner zone subfields were analysed.

Definition of outcomes and non-inferiority

The primary outcome was the change in CRT at 6 months. A secondary outcome was the change in VA at 6 months. Because relative change in macular thickening provides unstable data in eyes with mild degrees of baseline thickening, the absolute rather than the relative change in retinal thickness reduction was used,[9] and given the clinical importance of the central subfield, data analysis was weighted to this parameter using a simple algorithm: If subjects had a central subfield thickness $\geq$250 μm, then the central subfield was used in the analysis regardless of the thickness measurements in the inner subzones; if subjects had a central subfield < 250 μm, then the thickest of the four inner subzones was analysed. Both eyes of the subjects were potentially eligible, and the eye was the unit of statistical analysis.

Given that there are no consistently accepted definitions of 'diffuse' and 'focal' oedema and that there is no convincing evidence that this labelling predicts VA change or response to treatment,[10] eyes were not categorized by oedema type.

An analysis of covariance (ANCOVA) regression analysis with the 6-month retinal thickness as the dependent variable, and group and baseline retinal thickness as covariates was constructed, adjusting the variance calculations for any within-subject correlations. This analytic strategy adjusts for the effects of regression to the mean because of unequal baseline values, optimizes the precision of the estimates and reduces the sample size requirements. A similar analysis was performed with 6-month VA as the dependent variable and baseline acuity as a covariate. Assumptions of ANCOVA regression, and outlying and influential observations were assessed.

For the retinal thickness comparison, non-inferiority required the one-sided 95% confidence interval of the group covariate coefficient in the ANCOVA regression to be less than 35 ìm in favour of the control group. This is considered as the difference between group means after adjusting for regression to the mean. *This requirement was defined as the ΔOCT.*

For the VA comparison, non-inferiority required the one-sided 95% confidence interval of the group covariate coefficient in the ANCOVA regression to be less than 0.06 (three letters) in favour of the control group. *This requirement was defined as the ΔVA.*

Sample size calculation

The sample size was calculated to detect a difference of 35 μm with a one-sided 95% confidence interval at 80% power and alpha value of 0.05. The standard deviation (SD) was estimated from the literature as 60 μm.[7] The correlation between baseline and follow-up retinal thickness was estimated as 0.7. A sample size of 37 eyes was required. An increase in sample size of 15% in each group was added to allow for loss of follow-up or incomplete data.

Results

Patient allocation, losses to follow-up and exclusions are shown in Figure 1. There were 24 eyes allocated to the 2RT group. One patient died, and two withdrew (three eyes lost). One patient had a retinal vein occlusion during the study and was excluded prior to analysis. Hence, 20 eyes of 17 subjects in the 2RT group were analysed. There were 18 eyes of 14 subjects in the conventional group for analysis. There were 20 eyes allocated to the control group. One patient died, and one withdrew. There were two extreme observations (Fig. 2): one subject in the control group was a patient who developed cholecystitis and required surgery during the study; perioperatively, she changed diet and lost a large amount of weight. She had an extraordinary reduction in retinal thickness and was a highly influential observation on the regression analysis. There was one extreme outlier in the 2RT group but with no

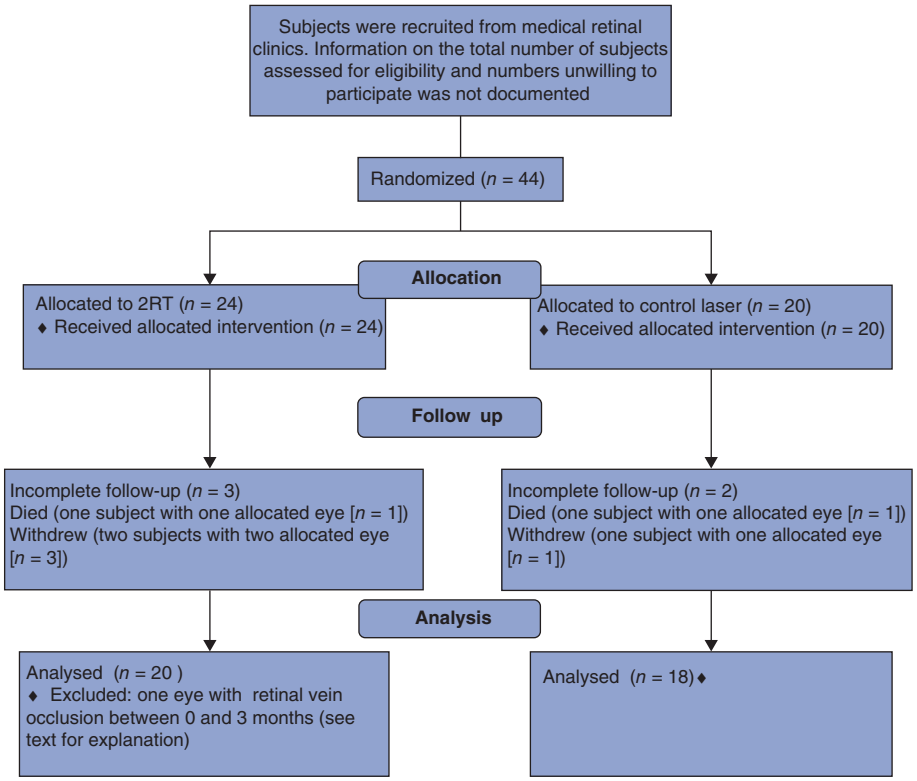

Figure 1. Flow diagram of patient randomization and analysis. 2RT, retinal regeneration therapy.

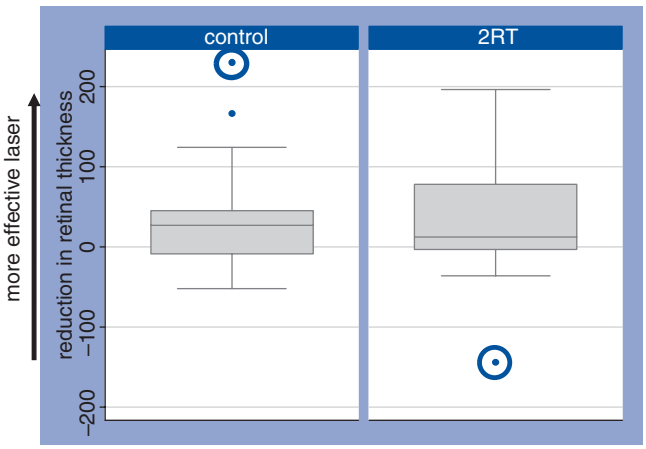

Figure 2. Boxplot of the reduction in retinal thickness at 6 months in both groups. The extreme outliers in each group are depicted (red circles). 2RT, retinal regeneration therapy.

Table 1. Baseline data

Variable	2RT	Controls
Number	20	18
Mean age (SD)	63.8 (9.6)	56.3 (9.3)
Male : female	13:7	15:3
Mean baseline CRT (SD)	330.1 (84.0)	323.2 (65.2)
Mean baseline VA (SD)	0.18 (.23)	0.13 (.24)
Mean baseline systolic BP (SD)	138.3 (12.2)	138.7 (19.3)
Mean baseline HbA1c (SD)	7.8 (1.3)	8.1 (1.37)
Mean change HbA1c (SD)	0.22 (.96)	−0.4 (1.6)
Re-treatment at 3 months	18	16
Mean change in CRT at 6 months* (SD)	40.5 (74.9)	34.6 (78.0)
Mean change in VA at 6 months** (SD)	0.01 (0.1)	0.01 (0.1)

*$P = 0.88$, **$P = 0.98$. 2RT, retinal regeneration therapy; BP, blood pressure; CRT, central retinal thickness in μm; HbA1c, haemoglobin A1c; SD, standard deviation; VA, logarithm of minimum angle of resolution visual acuity.

unusual clinical features. We have provided the analysis both with and without these data points. Subjects reported that the 2RT laser treatment was completely painless, and it was well tolerated.

Table 1 compares the baseline variables, and change in mean CRT and VA at 6 months in each group. The only variable that we considered to be prognostic was baseline CRT, which was adjusted for in the regression analysis. The 2RT group was older, with a mean age of 63.8 (SD 9.6) years compared with a mean age of 56.3 (SD 9.3) years in the control group. Men were overrepresented in both groups. Note that because of the randomization, any differences in distribution are due to chance; hence, the calculation of *P*-values is illogical, as discussed in the Consolidated Standards of Reporting Trials guidelines.

Figure 2 shows box plots of the change in retinal thickness for both groups. The distribution of both groups was similar. The outlying observations that were omitted from one of the regression analyses are

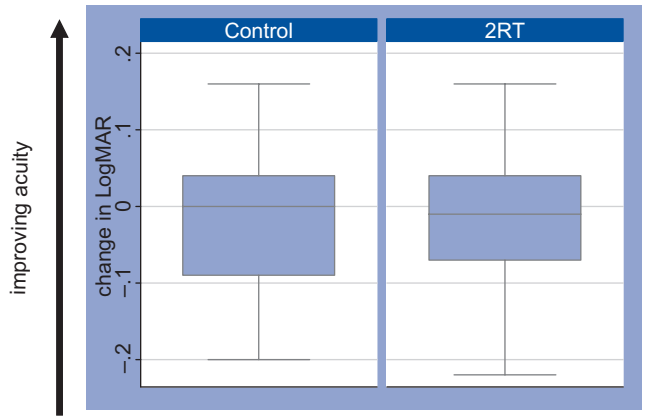

Figure 3. The visual acuity was stabilized in both groups with an almost identical distribution between groups. 2RT, retinal regeneration therapy.

circled in red in Figure 2. The outlier in the 2RT group had the largest studentized residual of the dataset (3.13) and was from a patient whose retinal thickness increased between 3 and 6 months, considerably reducing the mean reduction in this group. Figure 3 shows the box plots for change in VA for both groups. These plots were remarkably similar, with almost identical medians and distributions, indicating stability of VA in both groups.

The mean reduction in retinal thickness in the control group was 40.5 (SD 74.9) μm; the mean reduction in the 2RT group was 34.6 (SD 78.0) μm. However, adjusting for regression to the mean and the higher baseline retinal thickness of the 2RT group, the difference in retinal thickness reduction by ANCOVA was 10.9 (SD 17.6) μm in favour of the control laser. The ΔOCT was 40.8 μm. If the two extreme outliers are excluded, the mean reduction in retinal thickness in the control group was 27.8 (SD 57.9) μm; the mean reduction in the 2RT group was 44 (SD 67.0) μm. The difference in retinal thickness reduction by ANCOVA was 5.6 (SD14.2) μm in favour of the 2RT laser, and the ΔOCT was 18.5 μm. Hence, the primary null hypothesis is not unambiguously rejected.

The difference in VA change by ANCOVA was 0.02 (SD 0.04) in favour of 2RT. The ΔVA was 0.059 (three letters); hence, the secondary null hypothesis was rejected.

There were seven eyes that met the inclusion criteria of retinal thickness ≥300 μm in the inner subfield but had a retinal thickness of <250 μm in the central subfield. If the VA regression analysis was performed with these seven eyes omitted from the VA analysis, then the ΔVA inflates to 0.08 (four letters); but, the difference in VA change between groups remains approximately zero, and the increase in ΔVA is largely explained by an inflation of the standard error because of the reduced sample size in the subanalysis.

Representative colour fundus photos and FFAs of a patient before and 6 months after 2RT for DMO are shown in Figure 4.

Discussion

The results from this pilot study indicate that 2RT can be effectively used to treat DMO. Although no complications were noted in either the 2RT or control groups, the safety profile of 2RT has clinically important theoretical advantages over photocoagulative laser. Although the retinal pigment epithelium is the targeted tissue of photocoagulation, there is dissipation of heat to the surrounding tissue, particularly the overlying photoreceptors. For this reason, treatment of oedema close to or at the fovea is not performed. Damage to perifoveal photoreceptors can cause microperimetric defects, and burns can enlarge with time.

In 1983, Anderson and Parrish introduced the concept of 'selective photothermolysis'.[11] They showed that pigmented cells and organelles could be selectively targeted and that the thermal effects of short laser pulses could be spatially confined.[11] Roider *et al.* later applied this concept to retinal laser treatment.[12] This approach reduced the collateral damage to the sensory retina, as demonstrated by microperimtery, but still used a photocoagulative thermal insult.[13] Subthreshold micropulse diode laser has been used successfully to treat DMO[14] and appears comparable with argon laser treatment;[15] however, to our knowledge, randomized equivalence/non-inferiority studies have not been performed.

Latina and Park demonstrated that selective targeting of pigmented trabecular meshwork cells could be achieved with a 532 nm Q-switched neodymium-YAG laser at pulse durations between 10 ns and 1 μs without producing collateral thermal or structural damage to adjacent non-pigmented trabecular meshwork cells on electron microscopy.[16] This led to the development of selective laser trabeculoplasty for the treatment of elevated intraocular pressure. The concept was modified to produce 2RT, which uses a 532 nm Q-switched neodynium-YAG laser at a pulse duration of 3 ns and spot size fixed at 400 μm, and also includes a unique beam profile that finely distributes the delivered energy over the treatment spot. This laser is theoretically appealing for the treatment of the retinal pigment epithelium because it is highly selective. Light microscopic examination of treated rat retina demonstrates no overlying photoreceptor injury at clinically relevant

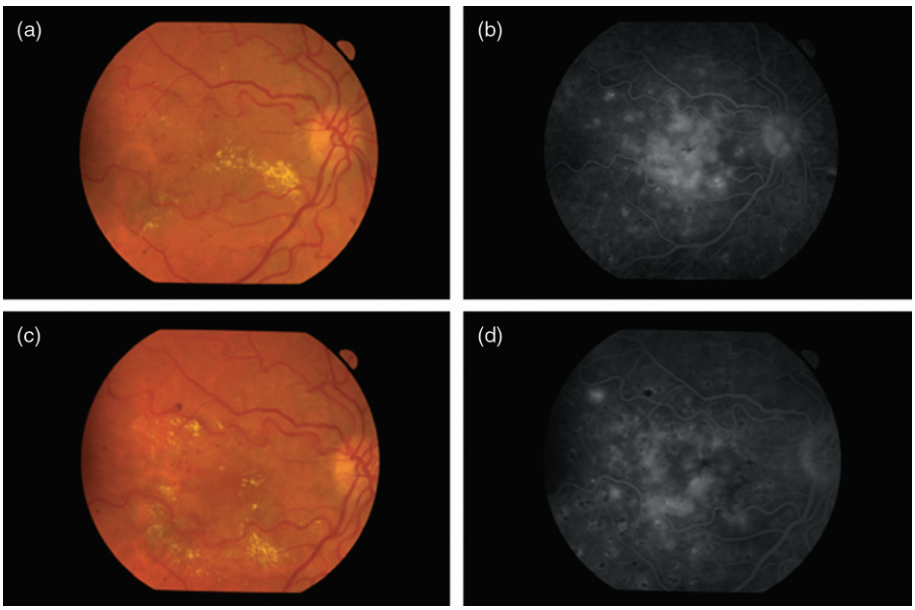

Figure 4. Representative colour fundus photos (a,c) and fluorescein angiograms (a,d) of a patient before and 6 months after retinal regeneration therapy for diabetic macular oedema. The subfoveal central retinal thickness reduced from 540 to 409 μm. But, note the persistence of perifoveal lipid (c).

energy settings with little inflammatory response. (Chidlow G, unpublished data, 2009).

The mechanism by which this new laser reduces retinal thickening in DMO remains unclear. However, the fact that conventional photocoagulative laser can effectively reduce DMO without directly treating leaking microaneurysms provides ample precedent for a generalized laser-induced effect on water permeability across the retina.[17–19]

There are a number of limitations to this study. First, the numbers are small, and the follow-up is short; we can provide no information about the longer term VA outcome. Second, the study was designed as a non-inferiority study rather than a superiority study. This has inherent problems. It does not lend itself to the traditional null hypothesis testing. To overcome this logical conundrum, a difference between outcomes that is considered as clinically equivalent (the Δ value) is assigned. For the reduction in CRT, we elected a Δ of 35 μm. One could argue that this Δ is too high, which 'every micron counts'; conversely, one could argue that this Δ is too small, which a greater difference is required to believe that the two lasers are clinically different in efficacy. However, clearly, the larger the Δ, the more likely equivalence will be demonstrated. We believed that a Δ of 35 μm had a reasonable evidence base and was the largest difference that we could easily defend. The value was chosen on a consensus of medical retinal opinion based on the fact that the test–retest repeatability of the Stratus OCT is approximately 10%;[20] hence, with an average baseline thickness of 350 μm, 35 μm would be at the upper limit of the repeatability. Differences less than that are arguably noise. Also, non-inferiority studies lack a placebo control. We believed it was unethical to have a placebo instead of an active control, but this is problematic in respect to the 'assay sensitivity' of the study.[21] It requires that the active control is performing to standard. There are limited data about the OCT-recorded change in retinal thickness after laser treatment for DMO. The absolute reduction as recorded in the current study depends on the baseline thickness, with thicker retinas showing more absolute thinning after laser. Based on available data from the literature, the average reduction in CRT after photocoagulation for mild-to-moderate DMO at 6 months was estimated at approximately 20–40 μm.[7,22] Hence, the mean reduction in CRT in our control group appears consistent with available data. Third, we did not record information about those patients that met eligibility criteria but did not consent to participate. This does not cause selection bias but conceivably affects the generalizability of the results; however, the subjects were recruited from medical retinal clinics, and we believe that they are likely to be representative of most developed world Caucasian populations. Fourth, a modified intention-to-treat analysis was performed rather than a strict intention to treat. We omitted one patient from the 2RT group who suffered a branch retinal vein occlusion. This patient had a superior temporal branch vein occlusion that occurred between visits. At the 6-month visit, the logarithm of minimum angle of resolution was 0.82. The vein occlusion was not in an area of previously thickened retina, and we have no reason to believe that it was a treatment-related event but cannot exclude this theoretical possibility. 2RT laser applications were evident on the FFAs as a zone of blocked fluorescence with peripheral staining. The histological substrate of this observation, in particular, whether or

not the sensory retina is damaged is unclear. Furthermore, the long-term outcome of these FFA features, in particular, whether or not they enlarge with time is unknown. The phenomenon potentially undermines the theoretic advantage of 2RT over conventional photocoagulation. Although an intention-to-treat design reduces potential bias and effectively answers the question of what happens when a patient is assigned to a particular treatment, it does not necessarily answer the question: What is the effect of treatment? We felt that given the small sample size and the fact that this was a random event, their inclusion was not sensible. Arguably, the optimal comparison of the two treatment modalities is depicted in the box plots in Figures 1 and 2.

So-called *post hoc* or observed power calculations were not performed because they are illogical.[23]

In conclusion, 2RT approximates the short-term efficacy of conventional photocoagulation in relation to reduction in macular oedema and stability of VA. We believe that the results from this study provide motivation for larger trials assessing the new laser technology for the treatment of macular oedema.

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